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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Carboxylic acid derivatives having 5 alpha-reductase inhibitory activity**

Carbonsäurederivate als 5-alpha-Reduktase-Inhibitor

Dérivés des acides carboxyliques comme inhibiteurs de 5-alpha-réductase

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EP-A- 0 291 245 **EP-A- 0 294 035**

- **CHEMICAL ABSTRACTS, vol. 103, no. 25, 13 December 1985, Columbus, Ohio, US; abstract no. 215005m, 'Carboxamide derivatives' page 865 ;**

EP 0 579 223 B1

Description

The present invention relates to novel carboxylic acid derivatives. More particularly, this invention relates to novel carboxylic acid derivatives having 5α-reductase inhibitory activity useful for treating benign prostatic hyperplasia, acne, seborrhea, female hirsutism, prostatic carcinoma, male alopecia, or the like, caused by excessive production of dihydrotestosterone (hereinafter referred to as "DHT").

Androgen dependent diseases which represent unfavorable physiological symptoms such as benign prostatic hyperplasia, acne, seborrhea, female hirsutism, male alopecia, or the like are caused by excessive accumulation of androgenic hormones in metabolic system.

It has long been known that DHT is essential for differentiation, development and maintenance of prostatic tissue. It has also been well known that the active androgen of male target organs such as prostate sebaceous gland, hair-root is DHT.

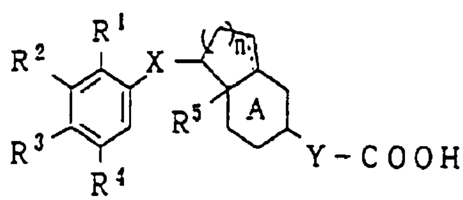
DHT is produced from testosterone by the action of a testosterone 5α-hydrogenating enzyme, "5α-reductase", in above target organs. Therefore, testosterone is a kind of pro-hormone in androgen-depending tissues such as prostate gland, and 5α-reductase plays an important role for the biosynthesis of DHT.

Importance of DHT concentration has recently been recognized in diseases which appear to be caused by an excess of male hormone, and a lot of 5α-reductase inhibitors have been reported, which include steroid derivatives such as 4-aza-steroid derivatives [JMC, 27, 1690 (1984)], 3-carboxylic acid steroid derivatives [Bioorganic chem, 17, 372 (1989)], JMC, 33, 937 (1990)], 3-phosphonic acid steroid derivatives [Japanese Patent Publication Kokai Hei 2-212499; Hei 2-225496], 3-sulfonic acid steroid derivatives [Japanese Patent Publication Kokai Hei 2-225494], 3-nitrosteroid derivatives [Japanese Patent Publication Kokai Hei 3-118325], non-steroid agents such as benzoylaminophenoxybutanoic acid derivatives [Japanese Patent Publication Kokai Hei 1-156950; Hei 1-139558], WS-9659 A and B originating from microorganisms [The Journal of Antibiotics, 1230, 1235, 1989], and the like.

The 5α-reductase inhibitors listed above are classified in two groups, namely steroid derivatives and non-steroid derivatives. The steroid derivatives have a problem of inducing side effects although they exhibit excellent pharmacological activities. On the other hand, non-steroid derivative having sufficient activity has not been discovered yet.

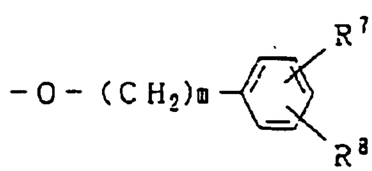
As the result of extensive study for providing non-steroid compounds having high activity as 5α-reductase inhibitors, the present inventors have found that specific carboxylic acid derivatives have an excellent activity. The present invention has been completed on the basis of such finding.

Thus, the present invention provides carboxylic acid derivatives of the following general formula (I):

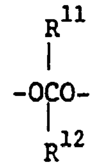


(I)

Wherein R^1, R^2, R^3 and R^4 each independently represent hydrogen atom, halogen atom, adamantyl group, optionally substituted C_1 - C_{14} alkyl group, optionally substituted C_3 - C_{10} cycloalkyl group, optionally substituted C_1 - C_{14} alkoxy group, optionally substituted heterocyclic group, - OR^6 (R^6 represents hydrogen atom, adamantyl group, optionally substituted C_3 - C_{10} cycloalkyl group or optionally substituted heterocyclic group), or a group of the formula:



wherein R^7 and R^8 each independently represent hydrogen atom, C_1 - C_6 alkyl group, C_3 - C_8 cycloalkyl group, - $CONR^9R^{10}$ (R^9 and R^{10} each independently represent hydrogen atom or C_1 - C_6 alkyl group) or, when R^7 and R^8 are adjacent, they may form C_1 - C_6 alkylene group, and m represents 0 or 1, or, the adjacent two substituents selected from R^1, R^2, R^3 and R^4 may form a group of the formula:

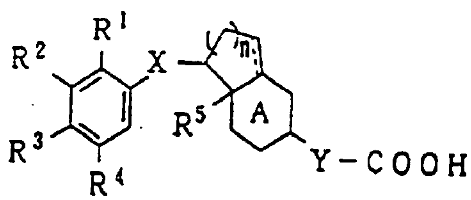


wherein R^{11} and R^{12} each independently represent hydrogen atom, C_1 - C_6 alkyl group or C_3 - C_8 cycloalkyl group or they may form, taken together, C_2 - C_8 alkylene group, a group of the formula: $-OCH_2CH_2O-$ or optionally substituted C_3 - C_4 alkylene group,

R^5 represents hydrogen atom or C_1 - C_5 alkyl group,
X represents $-CONR^{13}-$ or $-SO_2NR^{13}-$ (R^{13} represents hydrogen atom or C_1 - C_6 alkyl group),
Y represents a single bond, $-OCH_2-$ or $-CH=CH-$,
A ring may form benzene ring, cyclohexene ring or cyclohexadiene ring,
the dotted line represents a single bond or double bond, and
n represents 1 or 2, with the proviso that when the carbon atom to which R^5 is attached has a double bond, then R^5 is not present, or pharmaceutically acceptable salts thereof.

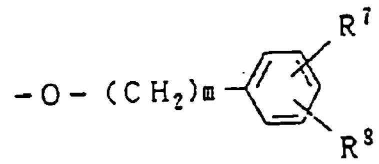
The present invention will be explained in detail below.

The present invention relates to the carboxylic acid derivatives of the following general formula (I):

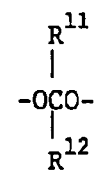


(I)

wherein R^1, R^2, R^3 and R^4 each independently represent hydrogen atom, halogen atom (iodine atom, fluorine atom, chlorine atom, bromine atom), adamantyl group, C_1 - C_{14} alkyl group (methyl group, pentyl group, nonyl group, tetradecyl group, etc.) optionally having one or more substituents selected from 5 or 6 membered heterocyclic ring containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as tetrahydrofuran ring, imidazoline ring, piperidine ring, dithian ring, thiomorpholine ring, etc., C_3 - C_{10} cycloalkyl group (cyclopropyl group, cyclohexyl group, cyclodecyl group, etc.) and adamantyl group, C_3 - C_{10} cycloalkyl group (cyclopropyl group, cyclohexyl group, cyclodecyl group, etc.) optionally having one or more substituents selected from C_1 -C_6 alkyl group (methyl group, butyl group, hexyl group, etc.), C_1 - C_{14} alkoxy group (methoxy group, pentyloxy group, nonyloxy group, tetradecyloxy group, etc.) optionally having one or more substituents selected from 5 or 6 membered heterocyclic ring containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as tetrahydrofuran ring, imidazoline ring, piperidine ring, dithian ring, thiomorpholine ring, etc.), C_3 - C_{10} cycloalkyl group (cyclopropyl group, cyclohexyl group, cyclodecyl group, etc.) and adamantyl group, 5 or 6 membered heterocyclic ring containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as tetrahydrofuran ring, imidazoline ring, piperidine ring, dithian ring, thiomorpholine ring, etc., optionally having one or more substituents selected from C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.), a group: $-OR^6$ {R^6 represents hydrogen atom, adamantyl group, C_3 - C_{10} cycloalkyl group (cyclopropyl group, cyclohexyl group, cyclodecyl group, etc.) optionally having one or more substituents selected from C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.) or 5 or 6 membered heterocyclic ring containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom (tetrahydrofuran ring, imidazoline ring, piperidine ring, dithian ring, thiomorpholine ring, etc.) optionally having one or more substituents selected from C_1 -C_6 alkyl group (methyl group, butyl group, hexyl group, etc.) and C_2 - C_6 acyl group (acetyl group, isobutyryl group, isovaleryl group, etc.)} or a group:



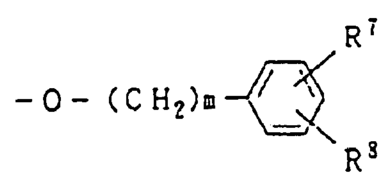
wherein R^7 and R^8 each independently represent hydrogen atom, C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.), C_3 - C_8 cycloalkyl group (cyclopropyl group, cyclohexyl group, cyclooctyl group, etc.), $-CONR^9R^{10}$ [R^9 and R^{10} each independently represent hydrogen atom or C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.), or, when R^7 and R^8 are adjacent, they may form C_1 - C_6 alkylene group (methylene group, trimethylene group, hexamethylene group, etc.), and m represents 0 or 1}, or, the two adjacent substituents selected from R^1, R^2, R^3 and R^4 may form a group of the formula:



wherein R^{11} and R^{12} each independently represent hydrogen atom, C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.) or C_3 - C_8 cycloalkyl group (cyclopropyl group, cyclopentyl group, cyclooctyl group, etc.) or, they may form C_2 - C_8 alkylene group (ethylene group, pentamethylene group, octamethylene group, etc.), a group: $-OCH_2CH_2O-$ or C_3 - C_4 alkylene group (trimethylene group, tetramethylene group) optionally having one or more substituents selected from C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.) and C_3 - C_8 cycloalkyl group (cyclopropyl group, cyclohexyl group, cyclooctyl group, etc.);

R^5 represents hydrogen atom or C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.), X represents $-CONR^{13}-$ or $-SO_2NR^{13}-$ [R^{13} represents hydrogen atom or C_1 - C_6 alkyl group (methyl group, butyl group, hexyl group, etc.)];
Y represents a single bond, $-OCH_2-$ or $-CH=CH-$;
A ring may form a benzene ring or cyclohexadiene ring;
the dotted line represents a single bond or double bond; and
n represents 1 or 2, with the proviso that, when the carbon to which R^5 is attached has a double bond, then R^5 is not present, or pharmaceutically acceptable salts thereof.

Of the compounds of the present invention, preferable is a compound of the formula (I) in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom; halogen atom; C_1 - C_{14} alkyl group optionally having one or more substituents selected from 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and C_3 - C_{10} cycloalkyl group; C_1 - C_{14} alkoxy group optionally having one or more C_3 - C_{10} cycloalkyl group; $-OR^6$ [R^6 represents C_3 - C_{10} cycloalkyl group optionally having one or more C_1 - C_6 alkyl group; or 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and optionally having one or more C_1 - C_6 alkyl groups] or a group of the formula:



wherein R^7 and R^8 each independently represent hydrogen atom, C_1 - C_6 alkyl group, C_3 - C_8 cycloalkyl group, -$CONR^9R^{10}$ (R^9 and R^{10} each independently represent hydrogen atom or C_1 - C_6 alkyl group) or, when R^7 and R^8 are adjacent, they may form C_1 - C_6 alkylene group, and m represents 0 or 1), R^5 represents C_1 - C_6 alkyl group, X represents -$CONR^{13}$- or -SO_2NR^{13}- (R^{13} represents hydrogen or C_1 - C_6 alkyl group), Y represents a single bond, -OCH_2-or -CH=CH-, A ring may form a benzene ring or cyclohexene ring, the dotted line represents a single bond or double bond, and n represents 1 or 2.

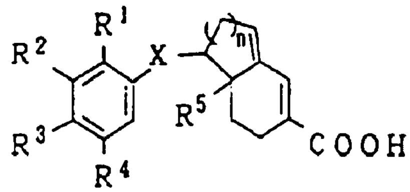
Particularly preferable is a compound of the formula (I) in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom; halogen atom; C_1 - C_{14} alkyl group optionally having one or more C_3 - C_{10} cycloalkyl groups; C_1 - C_{14} alkoxy group optionally having one or more C_3 - C_{10} cycloalkyl group; or -OR^6 (R^6 represents C_3 - C_{10} cycloalkyl group optionally having one or more C_1 - C_6 alkyl group); R^5 represents C_1 - C_6 alkyl group, X represents -$CONR^{13}$- (R^{13} represents hydrogen or C_1 - C_6 alkyl group); Y represents a single bond; A ring represents cyclo-hexene ring; the dotted line represents a single bond, and n represents 1 or 2.

Most preferable is a compound of the formula (I) in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom or C_1 - C_{14} alkoxy group; R^5 represents C_1 - C_6 alkyl group; X represents -$CONR^{13}$- (R^{13} represents hydrogen atom); Y represents a single bond; A ring represents a cyclohexene ring; the dotted line represents a double bond; and n represents 2.

The compounds of the general formula (I) above may contain an asymmetric carbon atom, and racemic mixture and optical isomers are included in the present invention.

The compounds of the present invention are illustrated in Tables 1 - 4 below.

Table 1



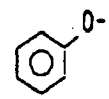
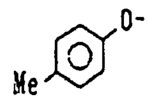
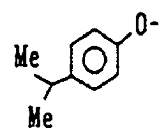
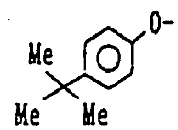
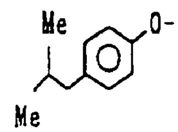
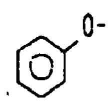
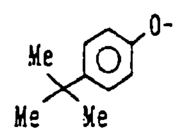
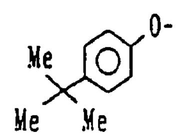
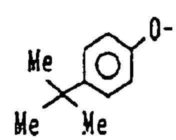
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
1	H	H		H	-Me	-CONH-	2
2	H	H		H	-Me	-CONH-	2
3	H	H		H	-Me	-CONH-	2
4	H	H		H	-Me	-CONH-	2
5	H	H		H	-Me	-CONH-	2
6	H	H		H	-Me	-CONMe-	2
7	H	H		H	-Me	-CONEt-	2
8	H	H		H	-Me	-CONH-	1
9	H	H		H	-Me	-CONMe-	1

Table 1 (continued)

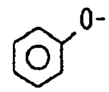
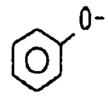
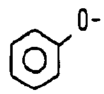
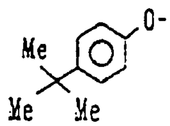
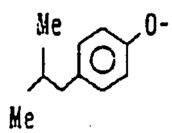
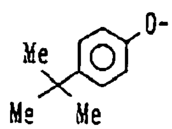
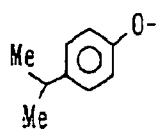
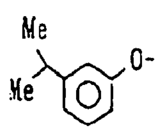
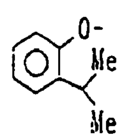
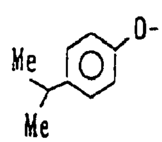
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
10	H		H	H	-Me	-CONH-	2
11	H		H	H	-Me	-CONH-	1
12		H	H	H	-Me	-CONH-	2
13		H	H	H	-Me	-CONH-	2
14		H	H	H	-Me	-CONH-	2
15		H	H	H	-Me	-CONH-	1
16	H		H	H	-Me	-CONH-	2
17	H		H	H	-Me	-CONH-	2
18	H		H	H	-Me	-CONH-	2
19	H		H	H	-Me	-CONMe-	2

Table 1 (continued)

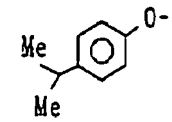
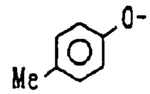
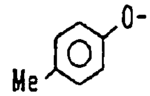
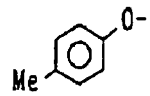
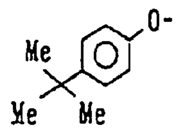
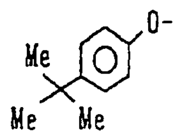
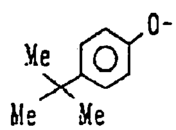
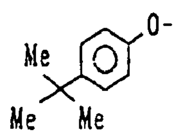
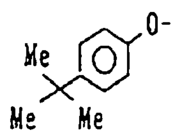
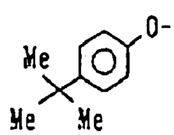
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
20	H		H	H	-Me	-CONH-	1
21	H		H	H	-Me	-CONH-	2
22	H		H	H	-Me	-CONH-	1
23	H		H	H	-Me	-CONMe-	2
24	H		H	H	-Me	-CONH-	2
25	H		H	H	-Me	-CONH-	1
26	H		H	H	-Me	-CONMe-	2
27	-OH		H	H	-Me	-CONH-	2
28	-Me		H	H	-Me	-CONH-	2
29	-Et		H	H	-Me	-CONH-	2

Table 1 (continued)

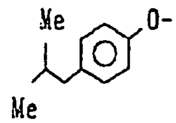
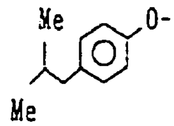
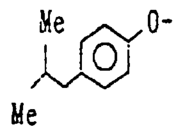
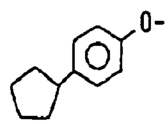
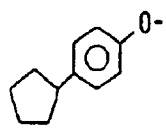
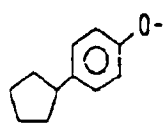
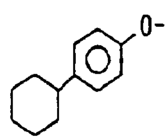
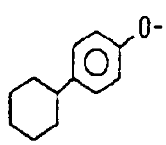
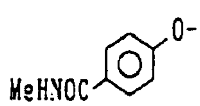
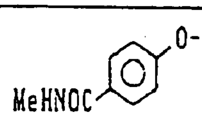
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
30	H		H	H	-Me	-CONH-	2
31	H		H	H	-Me	-CONH-	1
32	H		H	H	-Me	-CONMe-	2
33	H		H	H	-Me	-CONH-	2
34	H		H	H	-Me	-CONH-	1
35	H		H	H	-Me	-CONMe-	2
36	H		H	H	-Me	-CONH-	2
37	H		H	H	-Me	-CONH-	1
38	H		H	H	-Me	-CONH-	2
39	-Me		H	H	-Me	-CONH-	2

Table 1 (continued)

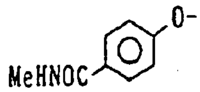
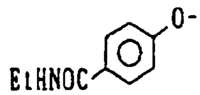
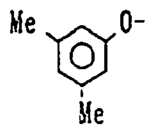
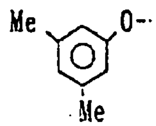
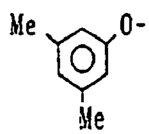
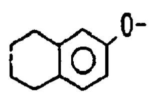
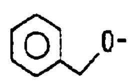
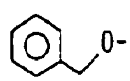
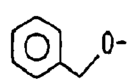
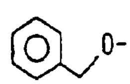
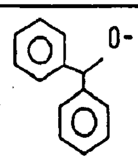
Compd. No.	R¹	R²	R³	R⁴	R⁵	X	n
40	H		H	H	-Me	-CONH-	1
41	H		H	H	-Me	-CONH-	2
42	H		H	H	-Me	-CONH-	2
43	H		H	H	-Me	-CONH-	1
44	-OH		H	H	-Me	-CONH-	2
45	H		H	H	-Me	-CONH-	2
46	H		H	H	-Me	-CONH-	2
47	-Me		H	H	-Me	-CONH-	2
48	-OH		H	H	-Me	-CONH-	2
49	H		H	H	-Me	-CONH-	1
50	H		H	H	-Me	-CONH-	2

Table 1 (continued)

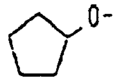
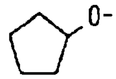
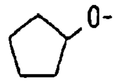
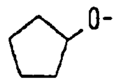
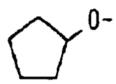
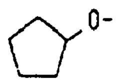
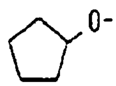
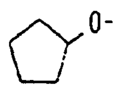
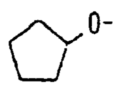
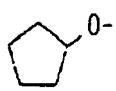
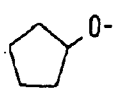
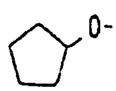
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
51	H		H	H	-Me	-CONH-	2
52	H		Me-	H	-Me	-CONH-	2
53	H		Et-	H	-Me	-CONH-	2
54	H		iPr-	H	-Me	-CONH-	2
55	H		Me-O-	H	-Me	-CONH-	2
56	H		Et-O-	H	-Me	-CONH-	2
57	H		iPr-	H	-Me	-CONH-	2
58	-OH		H	H	-Me	-CONH-	2
59	-F		H	H	-Me	-CONH-	2
60	-Cl		H	H	-Me	-CONH-	2
61	-Br		H	H	-Me	-CONH-	2
62	H		H	H	-Me	-CONH-	1

Table 1 (continued)

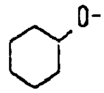
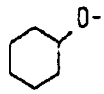
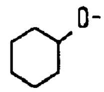
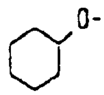
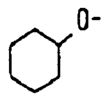
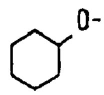
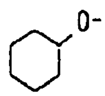
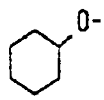
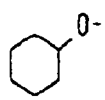
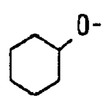
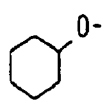
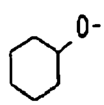
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
63	H		H	H	-Me	-CONH-	2
64	H		Me-	H	-Me	-CONH-	2
65	H		Et-	H	-Me	-CONH-	2
66	H		iPr-	H	-Me	-CONH-	2
67	H		Me-O-	H	-Me	-CONH-	2
68	H		Et-O-	H	-Me	-CONH-	2
69	H		iPr-O-	H	-Me	-CONH-	2
70	-OH		H	H	-Me	-CONH-	2
71	-Me		H	H	-Me	-CONH-	2
72	-F		H	H	-Me	-CONH-	2
73	-Cl		H	H	-Me	-CONH-	2
74	-Br		H	H	-Me	-CONH-	2

Table 1 (continued)

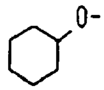
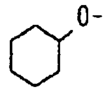
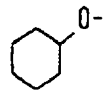
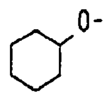
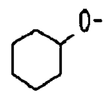
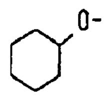
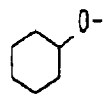
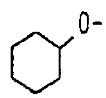
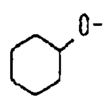
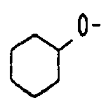
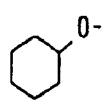
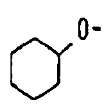
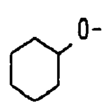
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
75	H		H	F-	-Me	-CONH-	2
76	H		H	Cl-	-Me	-CONH-	2
77	H		H	Br-	-Me	-CONH-	2
78	H		H		-Me	-CONH-	2
79	H		H	H	-Me	-CONMe-	2
80	H		Me-	H	-Me	-CONMe-	2
81	H		Et-	H	-Me	-CONMe-	2
82	H		iPr-	H	-Me	-CONMe-	2
83	H		Me-O-	H	-Me	-CONMe-	2
84	H		Et-O-	H	-Me	-CONMe-	2
85	H		iPr-O-	H	-Me	-CONMe-	2
86	-OH		H	H	-Me	-CONMe-	2

Table 1 (continued)

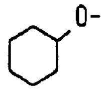
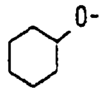
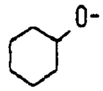
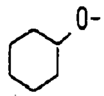
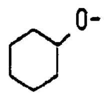
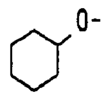
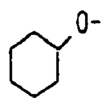
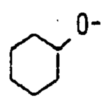
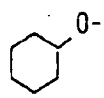
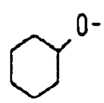
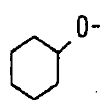
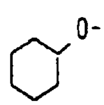
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
87	H		H	H	-Me	-CONH-	1
88	H		Me-	H	-Me	-CONH-	1
89	H		Et-	H	-Me	-CONH-	1
90	H		iPr-	H	-Me	-CONH-	1
91	H		Me-O-	H	-Me	-CONH-	1
92	H		Et-O-	H	-Me	-CONH-	1
93	H		iPr-O-	H	-Me	-CONH-	1
94	-OH		H	H	-Me	-CONH-	1
95	-Me		H	H	-Me	-CONH-	1
96	-F		H	H	-Me	-CONH-	1
97	-Cl		H	H	-Me	-CONH-	1
98	-Br		H	H	-Me	-CONH-	1

Table 1 (continued)

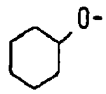
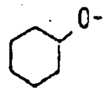
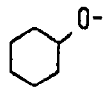
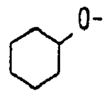
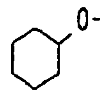
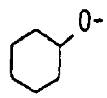
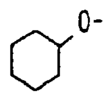
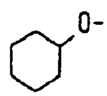
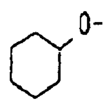
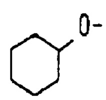
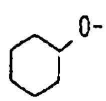
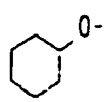
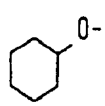
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
99	H		H	F-	-Me	-CONH-	1
100	H		H	Cl-	-Me	-CONH-	1
101	H		H	Br-	-Me	-CONH-	1
102	H		H		-Me	-CONH-	1
103	H		H	H	-Me	-CONMe-	1
104	H		Me-	H	-Me	-CONMe-	1
105	H		Et-	H	-Me	-CONMe-	1
106	H		iPr-	H	-Me	-CONMe-	1
107	H		Me-O-	H	-Me	-CONMe-	1
108	H		Et-O-	H	-Me	-CONMe-	1
109	H		iPr-O-	H	-Me	-CONMe-	1
110	-OH		H	H	-Me	-CONMe-	1

Table 1 (continued)

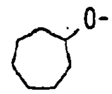
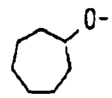
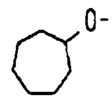
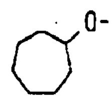
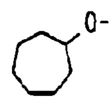
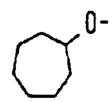
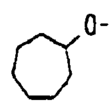
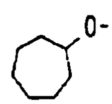
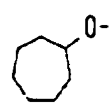
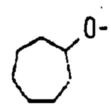
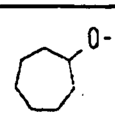
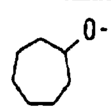
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
111	H		H	H	-Me	-CONH-	2
112	H		Me-	H	-Me	-CONH-	2
113	H		Et-	H	-Me	-CONH-	2
114	H		iPr-	H	-Me	-CONH-	2
115	H		Me-O-	H	-Me	-CONH-	2
116	H		Et-O-	H	-Me	-CONH-	2
117	H		iPr-O-	H	-Me	-CONH-	2
118	-OH		H	H	-Me	-CONH-	2
119	-Me		H	H	-Me	-CONH-	2
120	-F		H	H	-Me	-CONH-	2
121	-Cl		H	H	-Me	-CONH-	2
122	-Br		H	H	-Me	-CONH-	2

Table 1 (continued)

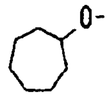
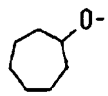
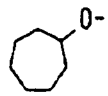
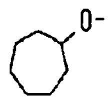
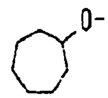
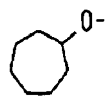
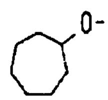
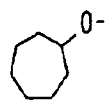
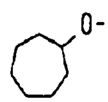
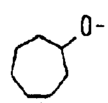
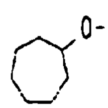
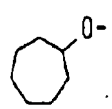
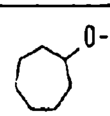
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
123	H		H	F-	-Me	-CONH-	2
124	H		H	Cl-	-Me	-CONH-	2
125	H		H	Br-	-Me	-CONH-	2
126	H		H		-Me	-CONH-	2
127	H		H	H	-Me	-CONMe-	2
128	H		Me-	H	-Me	-CONMe-	2
129	H		Et-	H	-Me	-CONMe-	2
130	H		iPr-	H	-Me	-CONMe-	2
131	H		Me-O-	H	-Me	-CONMe-	2
132	H		Et-O-	H	-Me	-CONMe-	2
133	H		iPr-O-	H	-Me	-CONMe-	2
134	-OH		H	H	-Me	-CONMe-	2

Table 1 (continued)

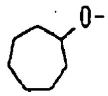
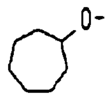
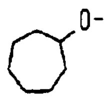
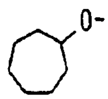
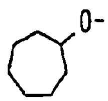
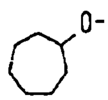
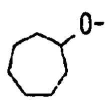
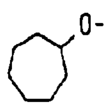
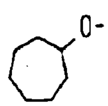
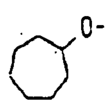
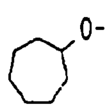
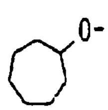
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
135	H		H	H	-Me	-CONH-	1
136	H		Me-	H	-Me	-CONH-	1
137	H		Et-	H	-Me	-CONH-	1
138	H		iPr-	H	-Me	-CONH-	1
139	H		Me-O-	H	-Me	-CONH-	1
140	H		Et-O-	H	-Me	-CONH-	1
141	H		iPr-O-	H	-Me	-CONH-	1
142	-OH		H	H	-Me	-CONH-	1
143	-Me		H	H	-Me	-CONH-	1
144	-F		H	H	-Me	-CONH-	1
145	-Cl		H	H	-Me	-CONH-	1
146	-Br		H	H	-Me	-CONH-	1

Table 1 (continued)

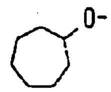
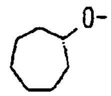
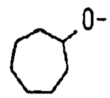
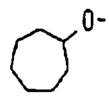
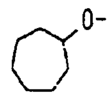
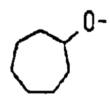
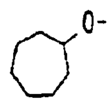
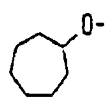
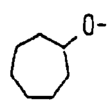
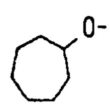
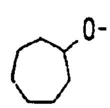
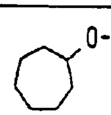
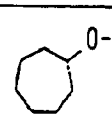
Compd. No.	R1	R2	R3	R4	R5	X	n
147	H		H	F-	-Me	-CONH-	1
148	H		H	Cl-	-Me	-CONH-	1
149	H		H	Br-	-Me	-CONH-	1
150	H		H		-Me	-CONH-	1
151	H		H	H	-Me	-CONMe-	1
152	H		Me-	H	-Me	-CONMe-	1
153	H		Et-	H	-Me	-CONMe-	1
154	H		iPr-	H	-Me	-CONMe-	1
155	H		Me-O-	H	-Me	-CONMe-	1
156	H		Et-O-	H	-Me	-CONMe-	1
157	H		iPr-O-	H	-Me	-CONMe-	1
158	-OH		H	H	-Me	-CONMe-	1

Table 1 (continued)

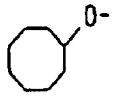
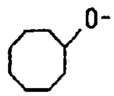
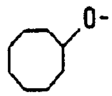
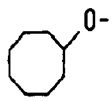
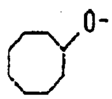
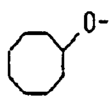
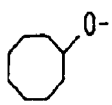
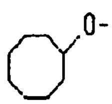
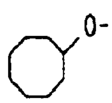
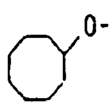
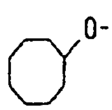
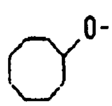
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
159	H		H	H	-Me	-CONH-	2
160	H		Me-	H	-Me	-CONH-	2
161	H		Et-	H	-Me	-CONH-	2
162	H		iPr-	H	-Me	-CONH-	2
163	H		Me-O-	H	-Me	-CONH-	2
164	H		Et-O-	H	-Me	-CONH-	2
165	H		iPr-O-	H	-Me	-CONH-	2
166	-OH		H	H	-Me	-CONH-	2
167	-Me		H	H	-Me	-CONH-	2
168	-F		H	H	-Me	-CONH-	2
169	-Cl		H	H	-Me	-CONH-	2
170	-Br		H	H	-Me	-CONH-	2

Table 1 (continued)

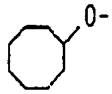
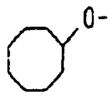
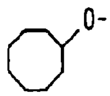
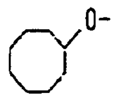
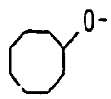
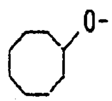
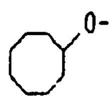
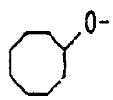
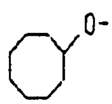
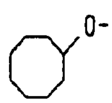
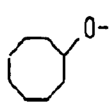
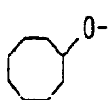
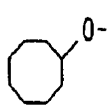
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
171	H		H	F-	-Me	-CONH-	2
172	H		H	Cl-	-Me	-CONH-	2
173	H		H	Br-	-Me	-CONH-	2
174	H		H		-Me	-CONH-	2
175	H		H	H	-Me	-CONMe-	2
176	H		Me-	H	-Me	-CONMe-	2
177	H		Et-	H	-Me	-CONMe-	2
178	H		iPr-	H	-Me	-CONMe-	2
179	H		Me-O-	H	-Me	-CONMe-	2
180	H		Et-O-	H	-Me	-CONMe-	2
181	H		iPr-O-	H	-Me	-CONMe-	2
182	-OH		H	H	-Me	-CONMe-	2

Table 1 (continued)

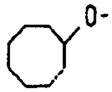
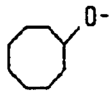
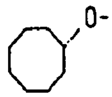
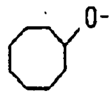
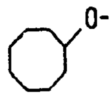
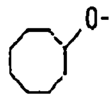
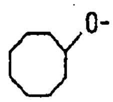
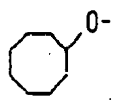
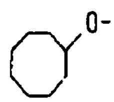
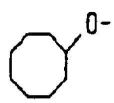
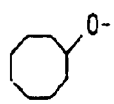
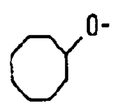
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
183	H		H	H	-Me	-CONH-	1
184	H		Me-	H	-Me	-CONH-	1
185	H		Et-	H	-Me	-CONH-	1
186	H		iPr-	H	-Me	-CONH-	1
187	H		Me-O-	H	-Me	-CONH-	1
188	H		Et-O-	H	-Me	-CONH-	1
189	H		iPr-O-	H	-Me	-CONH-	1
190	-OH		H	H	-Me	-CONH-	1
191	-Me		H	H	-Me	-CONH-	1
192	-F		H	H	-Me	-CONH-	1
193	-Cl		H	H	-Me	-CONH-	1
194	-Br		H	H	-Me	-CONH-	1

Table 1 (continued)

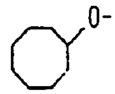
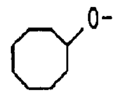
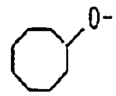
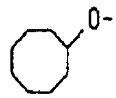
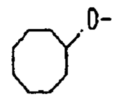
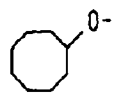
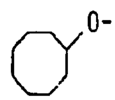
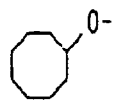
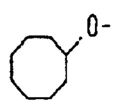
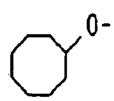
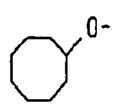
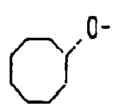
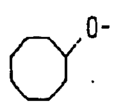
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
195	H		H	F-	-Me	-CONH-	1
196	H		H	Cl-	-Me	-CONH-	1
197	H		H	Br-	-Me	-CONH-	1
198	H		H		-Me	-CONH-	1
199	H		H	H	-Me	-CONMe-	1
200	H		Me-	H	-Me	-CONMe-	1
201	H		Et-	H	-Me	-CONMe-	1
202	H		iPr-	H	-Me	-CONMe-	1
203	H		Me-O-	H	-Me	-CONMe-	1
204	H		Et-O-	H	-Me	-CONMe-	1
205	H		iPr-O-	H	-Me	-CONMe-	1
206	-OH		H	H	-Me	-CONMe-	1

Table 1 (continued)

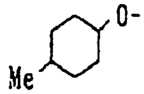
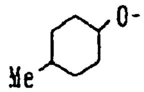
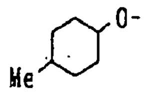
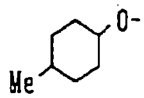
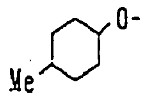
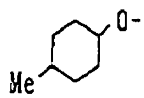
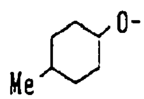
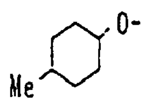
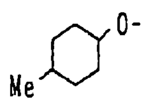
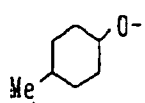
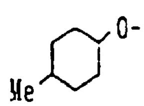
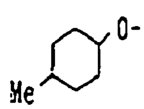
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
207	H		H	H	-Me	-CONH-	2
208	H		Me-	H	-Me	-CONH-	2
209	H		Et-	H	-Me	-CONH-	2
210	H		iPr-	H	-Me	-CONH-	2
211	H		Me-O-	H	-Me	-CONH-	2
212	H		Et-O-	H	-Me	-CONH-	2
213	H		iPr-O-	H	-Me	-CONH-	2
214	-OH		H	H	-Me	-CONH-	2
215	-Me		H	H	-Me	-CONH-	2
216	-F		H	H	-Me	-CONH-	2
217	-Cl		H	H	-Me	-CONH-	2
218	-Br		H	H	-Me	-CONH-	2

Table 1 (continued)

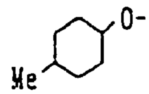
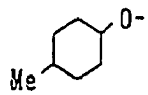
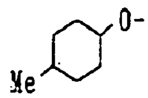
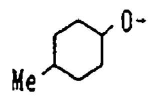
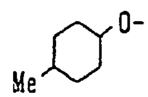
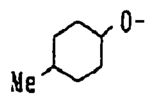
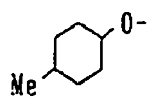
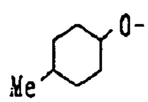
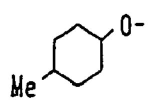
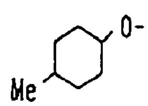
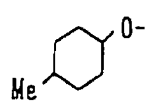
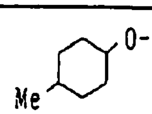
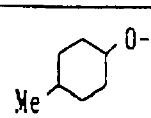
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
219	H		H	F-	-Me	-CONH-	2
220	H		H	Cl-	-Me	-CONH-	2
221	H		H	Br-	-Me	-CONH-	2
222	H		H		-Me	-CONH-	2
223	H		H	H	-Me	-CONMe-	2
224	H		Me-	H	-Me	-CONMe-	2
225	H		Et-	H	-Me	-CONMe-	2
226	H		iPr-	H	-Me	-CONMe-	2
227	H		Me-O-	H	-Me	-CONMe-	2
228	H		Et-O-	H	-Me	-CONMe-	2
229	H		iPr-O-	H	-Me	-CONMe-	2
230	-OH		H	H	-Me	-CONMe-	2

Table 1 (continued)

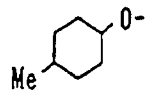
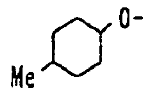
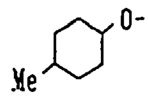
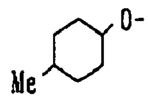
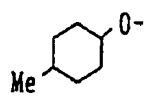
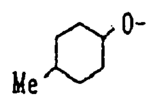
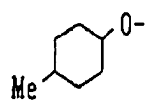
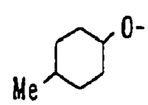
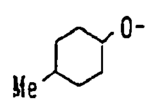
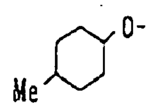
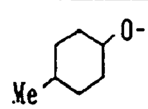
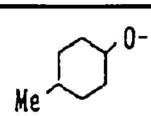
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
231	H		H	H	-Me	-CONH-	1
232	H		Me-	H	-Me	-CONH-	1
233	H		Et-	H	-Me	-CONH-	1
234	H		iPr-	H	-Me	-CONH-	1
235	H		Me-O-	H	-Me	-CONH-	1
236	H		Et-O-	H	-Me	-CONH-	1
237	H		iPr-O-	H	-Me	-CONH-	1
238	-OH		H	H	-Me	-CONH-	1
239	-Me		H	H	-Me	-CONH-	1
240	-F		H	H	-Me	-CONH-	1
241	-Cl		H	H	-Me	-CONH-	1
242	-Br		H	H	-Me	-CONH-	1

Table 1 (continued)

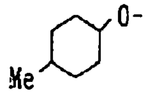
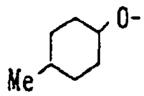
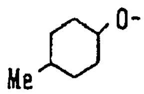
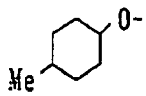
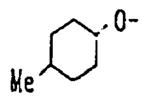
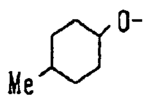
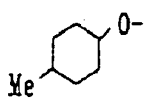
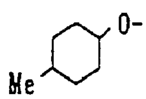
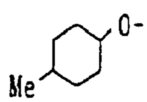
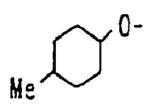
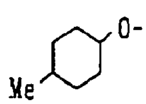
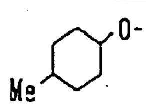
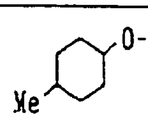
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
243	H		H	F-	-Me	-CONH-	1
244	H		H	Cl-	-Me	-CONH-	1
245	H		H	Br-	-Me	-CONH-	1
246	H		H		-Me	-CONH-	1
247	H		H	H	-Me	-CONMe-	1
248	H		Me-	H	-Me	-CONMe-	1
249	H		Et-	H	-Me	-CONMe-	1
250	H		iPr-	H	-Me	-CONMe-	1
251	H		Me-O-	H	-Me	-CONMe-	1
252	H		Et-O-	H	-Me	-CONMe-	1
253	H		iPr-O-	H	-Me	-CONMe-	1
254	-OH		H	H	-Me	-CONMe-	1

Table 1 (continued)

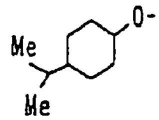
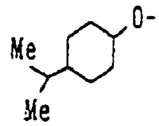
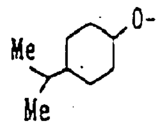
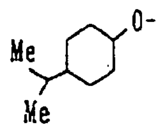
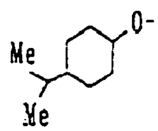
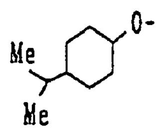
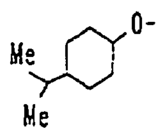
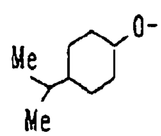
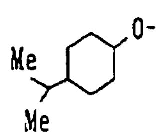
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
255	H		H	H	-Me	-CONH-	2
256	H		Me-	H	-Me	-CONH-	2
257	H		Et-	H	-Me	-CONH-	2
258	H		iPr-	H	-Me	-CONH-	2
259	H		Me-O-	H	-Me	-CONH-	2
260	H		Et-O-	H	-Me	-CONH-	2
261	H		iPr-O-	H	-Me	-CONH-	2
262	-OH		H	H	-Me	-CONH-	2
263	-Me		H	H	-Me	-CONH-	2

Table 1 (continued)

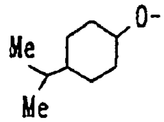
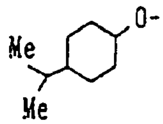
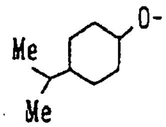
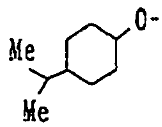
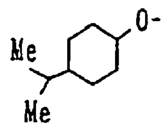
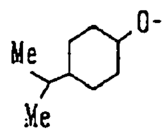
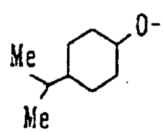
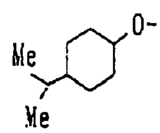
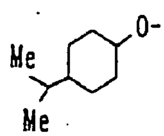
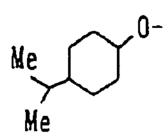
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
264	-F		H	H	-Me	-CONH-	2
265	-Cl		H	H	-Me	-CONH-	2
266	-Br		H	H	-Me	-CONH-	2
267	H		H	F-	-Me	-CONH-	2
268	H		H	Cl-	-Me	-CONH-	2
269	H		H	Br-	-Me	-CONH-	2
270	H		H		-Me	-CONH-	2
271	H		H	H	-Me	-CONMe-	2
272	H		Me-	H	-Me	-CONMe-	2

Table 1 (continued)

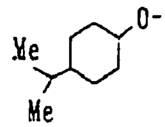
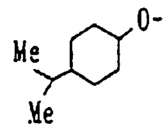
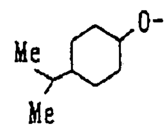
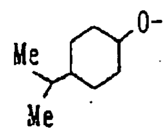
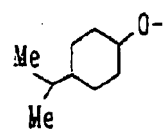
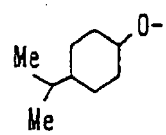
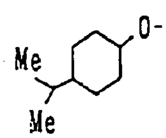
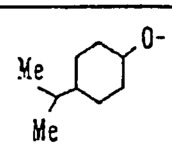
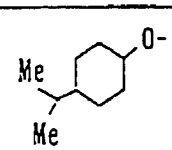
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
273	H		Et-	H	-Me	-CONMe-	2
274	H		iPr-	H	-Me	-CONMe-	2
275	H		Me-O-	H	-Me	-CONMe-	2
276	H		Et-O-	H	-Me	-CONMe-	2
277	H		iPr-O-	H	-Me	-CONMe-	2
278	-OH		H	H	-Me	-CONMe-	2
279	H		H	H	-Me	-CONH-	1
280	H		Me-	H	-Me	-CONH-	1
281	H		Et-	H	-Me	-CONH-	1

Table 1 (continued)

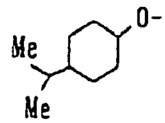
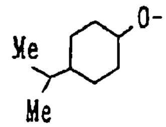
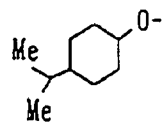
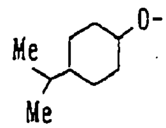
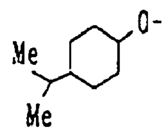
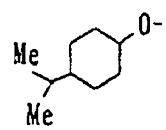
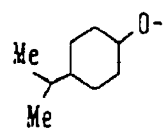
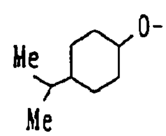
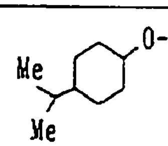
Compd. No.	R¹	R²	R³	R⁴	R⁵	X	n
282	H		iPr-	H	-Me	-CONH-	1
283	H		Me-O-	H	-Me	-CONH-	1
284	H		Et-O-	H	-Me	-CONH-	1
285	H		iPr-O-	H	-Me	-CONH-	1
286	-OH		H	H	-Me	-CONH-	1
287	-Me		H	H	-Me	-CONH-	1
288	-F		H	H	-Me	-CONH-	1
289	-Cl		H	H	-Me	-CONH-	1
290	-Br		H	H	-Me	-CONH-	1

Table 1 (continued)

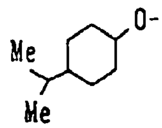
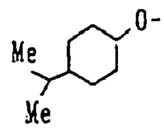
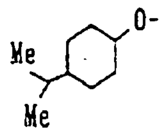
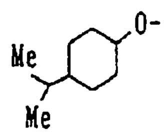
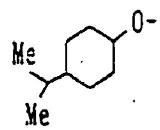
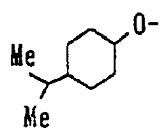
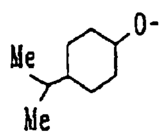
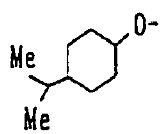
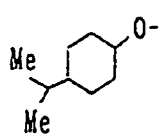
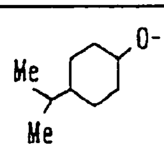
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
291	H		H	F-	-Me	-CONH-	1
292	H		H	Cl-	-Me	-CONH-	1
293	H		H	Br-	-Me	-CONH-	1
294	H		H		-Me	-CONH-	1
295	H		H	H	-Me	-CONMe-	1
296	H		Me-	H	-Me	-CONMe-	1
297	H		Et-	H	-Me	-CONMe-	1
298	H		iPr-	H	-Me	-CONMe-	1
299	H		Me-O-	H	-Me	-CONMe-	1

Table 1 (continued)

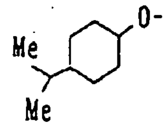
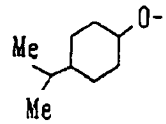
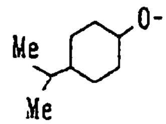
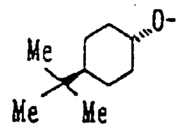
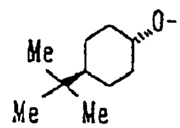
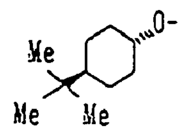
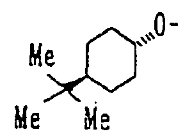
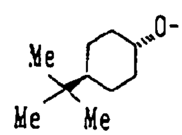
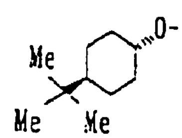
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
300	H		Et-O-	H	-Me	-CONMe-	1
301	H		iPr-O-	H	-Me	-CONMe-	1
302	-OH		H	H	-Me	-CONMe-	1
303	H		H	H	-Me	-CONH-	2
304	H		Me-	H	-Me	-CONH-	2
305	H		Et-	H	-Me	-CONH-	2
306	H		iPr-	H	-Me	-CONH-	2
307	H		Me-O-	H	-Me	-CONH-	2
308	H		Et-O-	H	-Me	-CONH-	2

Table 1 (continued)

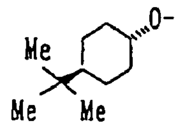
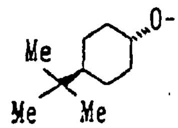
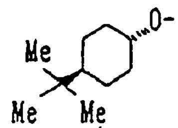
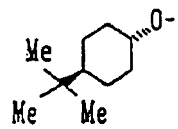
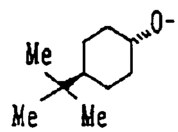
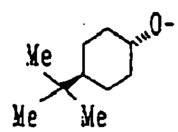
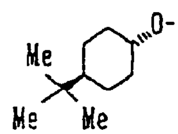
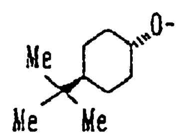
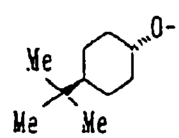
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
309	H		iPr-O-	H	-Me	-CONH-	2
310	-OH		H	H	-Me	-CONH-	2
311	-Me		H	H	-Me	-CONH-	2
312	-F		H	H	-Me	-CONH-	2
313	-Cl		H	H	-Me	-CONH-	2
314	-Br		H	H	-Me	-CONH-	2
315	H		H	F-	-Me	-CONH-	2
316	H		H	Cl-	-Me	-CONH-	2
317	H		H	Br-	-Me	-CONH-	2

Table 1 (continued)

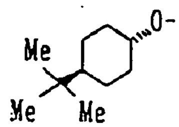
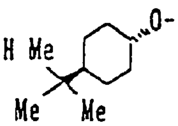
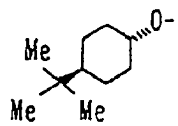
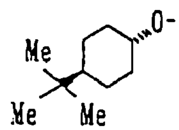
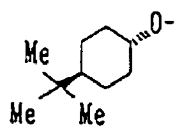
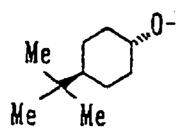
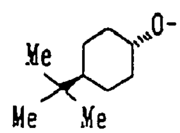
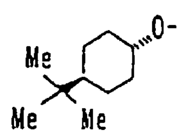
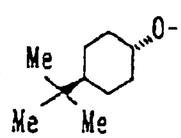
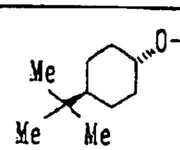
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
318	H		H		-Me	-CONH-	2
319	H		H	H	-Me	-CONMe-	2
320	H		Me-	H	-Me	-CONMe-	2
321	H		Et-	H	-Me	-CONMe-	2
322	H		iPr-	H	-Me	-CONMe-	2
323	H		Me-O-	H	-Me	-CONMe-	2
324	H		Et-O-	H	-Me	-CONMe-	2
325	H		iPr-O-	H	-Me	-CONMe-	2
326	-OH		H	H	-Me	-CONMe-	2

Table 1 (continued)

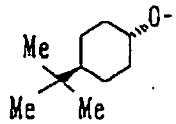
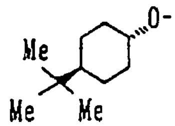
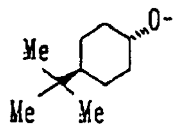
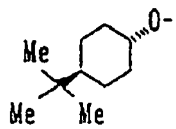
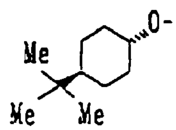
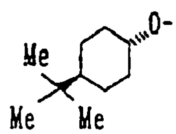
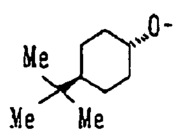
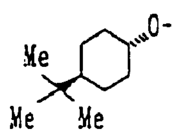
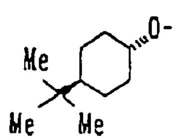
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
327	H		H	H	-Me	-CONH-	1
328	H		Me-	H	-Me	-CONH-	1
329	H		Et-	H	-Me	-CONH-	1
330	H		iPr-	H	-Me	-CONH-	1
331	H		Me-O-	H	-Me	-CONH-	1
332	H		Et-O-	H	-Me	-CONH-	1
333	H		iPr-O-	H	-Me	-CONH-	1
334	-OH		H	H	-Me	-CONH-	1
335	-Me		H	H	-Me	-CONH-	1

Table 1 (continued)

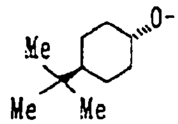
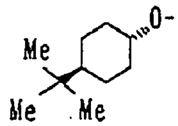
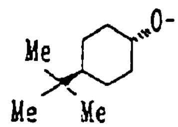
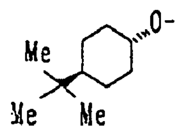
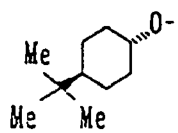
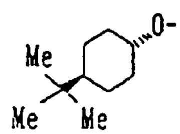
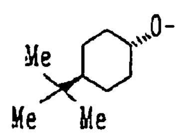
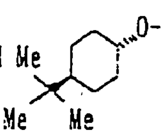
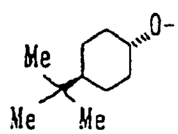
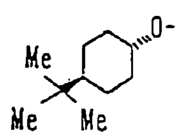
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
336	-F		H	H	-Me	-CONH-	1
337	-Cl		H	H	-Me	-CONH-	1
338	-Br		H	H	-Me	-CONH-	1
339	H		H	F-	-Me	-CONH-	1
340	H		H	Cl-	-Me	-CONH-	1
341	H		H	Br-	-Me	-CONH-	1
342	H		H		-Me	-CONH-	1
343	H		H	H	-Me	-CONMe-	1
344	H		Me-	H	-Me	-CONMe-	1

Table 1 (continued)

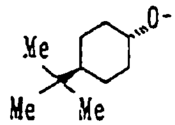
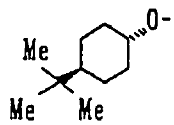
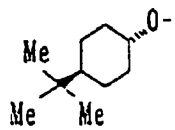
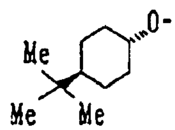
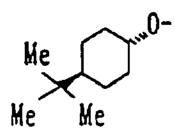
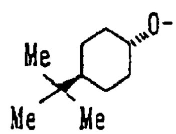
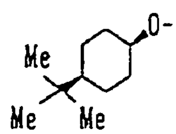
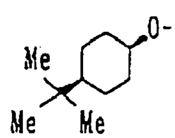
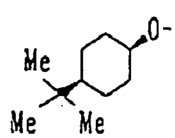
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
345	H		Et-	H	-Me	-CONMe-	1
346	H		iPr-	H	-Me	-CONMe-	1
347	H		Me-O-	H	-Me	-CONMe-	1
348	H		Et-O-	H	-Me	-CONMe-	1
349	H		iPr-O-	H	-Me	-CONMe-	1
350	-OH		H	H	-Me	-CONMe-	1
351	H		H	H	-Me	-CONH-	2
352	H		Me-	H	-Me	-CONH-	2
353	H		Et-	H	-Me	-CONH-	2

Table 1 (continued)

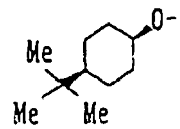
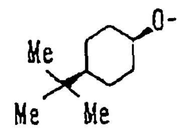
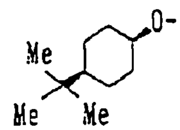
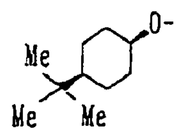
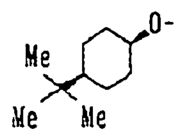
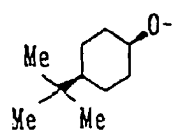
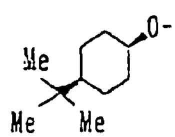
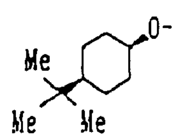
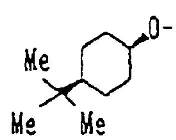
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
354	H		iPr-	H	-Me	-CONH-	2
355	H		Me-O-	H	-Me	-CONH-	2
356	H		Et-O-	H	-Me	-CONH-	2
357	H		iPr-O-	H	-Me	-CONH-	2
358	-OH		H	H	-Me	-CONH-	2
359	-Me		H	H	-Me	-CONH-	2
360	-F		H	H	-Me	-CONH-	2
361	-Cl		H	H	-Me	-CONH-	2
362	-Br		H	H	-Me	-CONH-	2

Table 1 (continued)

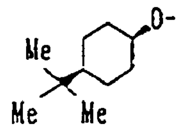
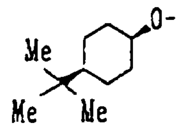
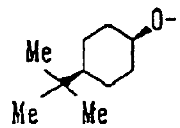
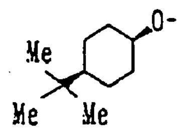
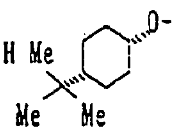
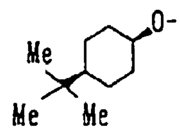
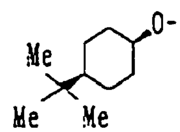
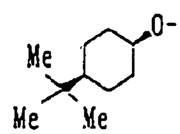
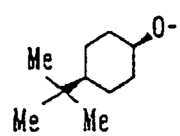
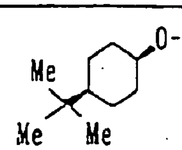
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
363	H		H	F-	-Me	-CONH-	2
364	H		H	Cl-	-Me	-CONH-	2
365	H		H	Br-	-Me	-CONH-	2
366	H		H		-Me	-CONH-	2
367	H		H	H	-Me	-CONMe-	2
368	H		Me-	H	-Me	-CONMe-	2
369	H		Et-	H	-Me	-CONMe-	2
370	H		iPr-	H	-Me	-CONMe-	2
371	H		Me-O-	H	-Me	-CONMe-	2

Table 1 (continued)

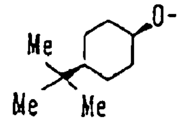
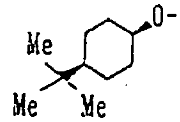
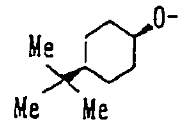
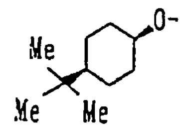
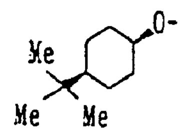
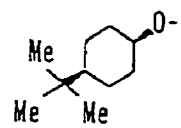
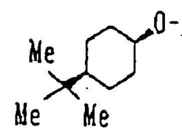
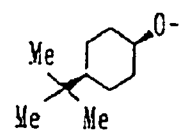
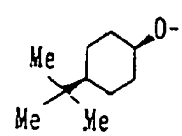
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
372	H		Et-O-	H	-Me	-CONMe-	2
373	H		iPr-O-	H	-Me	-CONMe-	2
374	-OH		H	H	-Me	-CONMe-	2
375	H		H	H	-Me	-CONH-	1
376	H		Me-	H	-Me	-CONH-	1
377	H		Et-	H	-Me	-CONH-	1
378	H		iPr-	H	-Me	-CONH-	1
379	H		Me-O-	H	-Me	-CONH-	1
380	H		Et-O-	H	-Me	-CONH-	1

Table 1 (continued)

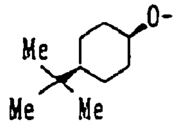
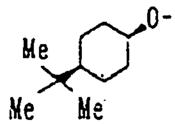
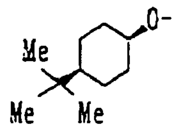
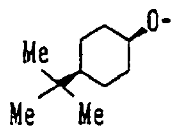
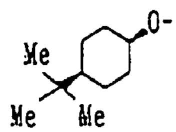
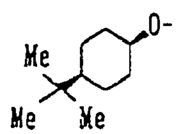
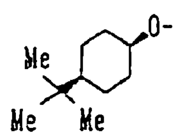
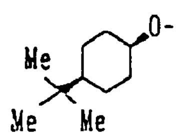
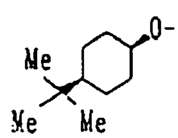
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
381	H		iPr-O-	H	-Me	-CONH-	1
382	-OH		H	H	-Me	-CONH-	1
383	-Me		H	H	-Me	-CONH-	1
384	-F		H	H	-Me	-CONH-	1
385	-Cl		H	H	-Me	-CONH-	1
386	-Br		H	H	-Me	-CONH-	1
387	H		H	F-	-Me	-CONH-	1
388	H		H	Cl-	-Me	-CONH-	1
389	H		H	Br-	-Me	-CONH-	1

Table 1 (continued)

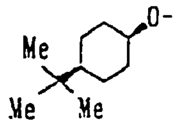
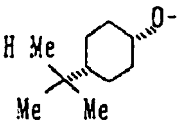
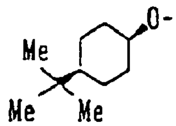
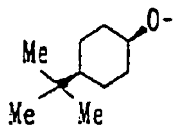
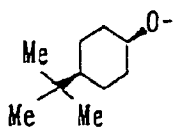
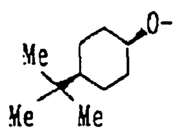
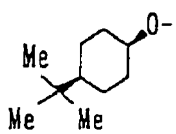
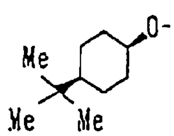
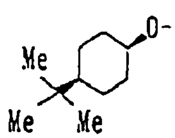
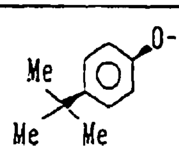
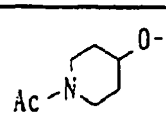
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
390	H		H		-Me	-CONH-	1
391	H		H	H	-Me	-CONMe-	1
392	H		Me-	H	-Me	-CONMe-	1
393	H		Et-	H	-Me	-CONMe-	1
394	H		iPr-	H	-Me	-CONMe-	1
395	H		Me-O-	H	-Me	-CONMe-	1
396	H		Et-O-	H	-Me	-CONMe-	1
397	H		iPr-O-	H	-Me	-CONMe-	1
398	-OH		H	H	-Me	-CONMe-	1
399	H		H	H	-Me	-CONH-	2

Table 1 (continued)

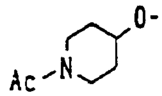
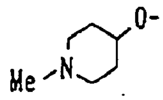
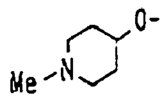
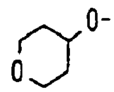
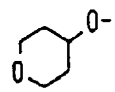
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
400	H		H	H	-Me	-CONH-	1
401	H		H	H	-Me	-CONH-	2
402	H		H	H	-Me	-CONH-	1
403	H		H	H	-Me	-CONH-	2
404	H		H	H	-Me	-CONH-	1
405	H	Me-	H	H	-Me	-CONH-	2
406	H	Et-	H	H	-Me	-CONH-	2
407	H	nPr-	H	H	-Me	-CONH-	2
408	H	iPr-	H	H	-Me	-CONH-	2
409	H	Me-O-	H	H	-Me	-CONH-	2
410	H	Et-O-	H	H	-Me	-CONH-	2
411	H	nPr-O-	H	H	-Me	-CONH-	2

Table 1 (continued)

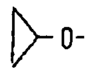
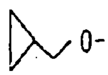
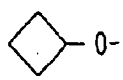
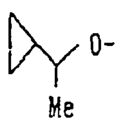
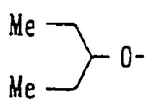
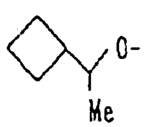
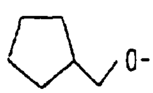
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
412	H	iPr-O-	H	H	-Me	-CONH-	2
413	H		H	H	-Me	-CONH-	2
414	H	nBu-O-	H	H	-Me	-CONH-	2
415	H	iBu-O-	H	H	-Me	-CONH-	2
416	H		H	H	-Me	-CONH-	2
417	H		H	H	-Me	-CONH-	2
418	H		H	H	-Me	-CONH-	2
419	H		H	H	-Me	-CONH-	2
420	H		H	H	-Me	-CONH-	2
421	H		H	H	-Me	-CONH-	2
422	H		H	H	-Me	-CONH-	2

Table 1 (continued)

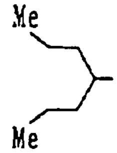
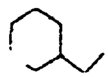
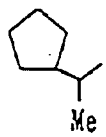
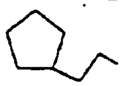
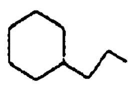
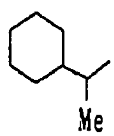
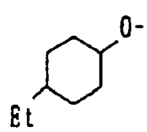
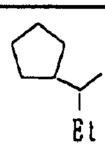
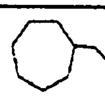
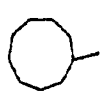
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
423	H	 O-	H	H	-Me	-CONH-	2
424	H	 O-	H	H	-Me	-CONH-	2
425	H	 O-	H	H	-Me	-CONH-	2
426	H	 O-	H	H	-Me	-CONH-	2
427	H	 O-	H	H	-Me	-CONH-	2
428	H	 O-	H	H	-Me	-CONH-	2
429	H		H	H	-Me	-CONH-	2
430	H	 O-	H	H	-Me	-CONH-	2
431	H	 O-	H	H	-Me	-CONH-	2
432	H	 O-	H	H	-Me	-CONH-	2

Table 1 (continued)

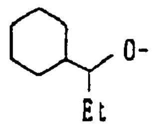
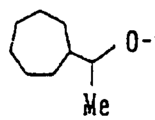
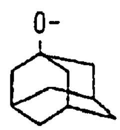
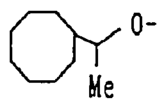
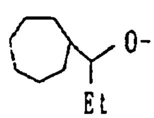
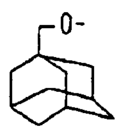
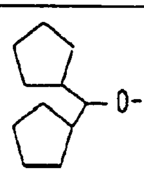
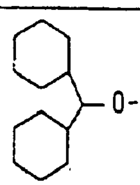
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
433	H		H	H	-Me	-CONH-	2
434	H		H	H	-Me	-CONH-	2
435	H		H	H	-Me	-CONH-	2
436	H		H	H	-Me	-CONH-	2
437	H		H	H	-Me	-CONH-	2
438	H		H	H	-Me	-CONH-	2
439	H		H	H	-Me	-CONH-	2
440	H		H	H	-Me	-CONH-	2
441	H		H	H	-Me	-CONH-	2
442	H		H	H	-Me	-CONH-	2

Table 1 (continued)

Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
443	H	Me-	H	H	-Me	-CONH-	1
444	H	Et-	H	H	-Me	-CONH-	1
445	H	nPr-	H	H	-Me	-CONH-	1
446	H	iPr-	H	H	-Me	-CONH-	1
447	H	Me-O-	H	H	-Me	-CONH-	1
448	H	Et-O-	H	H	-Me	-CONH-	1
449	H	nPr-O-	H	H	-Me	-CONH-	1
450	H	iPr-O-	H	H	-Me	-CONH-	1
451	H	 O-	H	H	-Me	-CONH-	1
452	H	nBu-O-	H	H	-Me	-CONH-	1
453	H	iBu-O-	H	H	-Me	-CONH-	1
454	H	 O-	H	H	-Me	-CONH-	1

Table 1 (continued)

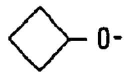
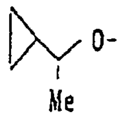
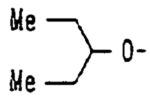
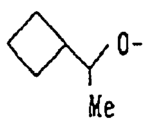
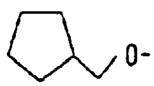
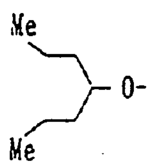
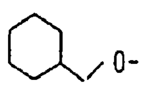
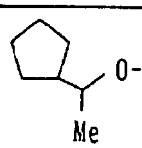
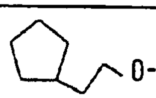
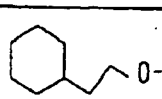
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
455	H		H	H	-Me	-CONH-	1
456	H		H	H	-Me	-CONH-	1
457	H		H	H	-Me	-CONH-	1
458	H		H	H	-Me	-CONH-	1
459	H		H	H	-Me	-CONH-	1
460	H		H	H	-Me	-CONH-	1
461	H		H	H	-Me	-CONH-	1
462	H		H	H	-Me	-CONH-	1
463	H		H	H	-Me	-CONH-	1
464	H		H	H	-Me	-CONH-	1
465	H		H	H	-Me	-CONH-	1

Table 1 (continued)

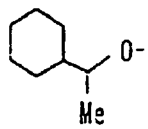
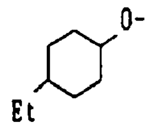
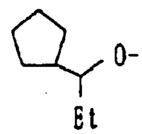
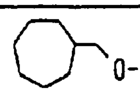
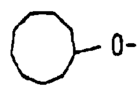
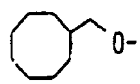
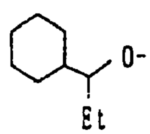
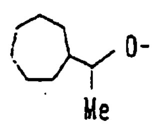
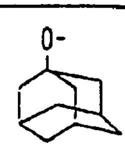
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
466	H		H	H	-Me	-CONH-	1
467	H		H	H	-Me	-CONH-	1
468	H		H	H	-Me	-CONH-	1
469	H		H	H	-Me	-CONH-	1
470	H		H	H	-Me	-CONH-	1
471	H		H	H	-Me	-CONH-	1
472	H		H	H	-Me	-CONH-	1
473	H		H	H	-Me	-CONH-	1
474	H		H	H	-Me	-CONH-	1
475	H		H	H	-Me	-CONH-	1

Table 1 (continued)

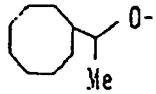
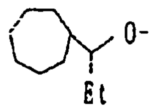
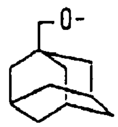
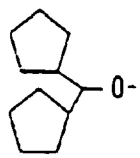
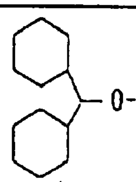
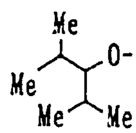
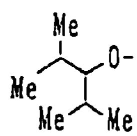
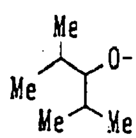
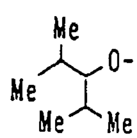
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
476	H		H	H	-Me	-CONH-	1
477	H		H	H	-Me	-CONH-	1
478	H		H	H	-Me	-CONH-	1
479	H		H	H	-Me	-CONH-	1
480	H		H	H	-Me	-CONH-	1
481	H		H	H	-Me	-CONH-	2
482	H		Me-	H	-Me	-CONH-	2
483	H		Et-	H	-Me	-CONH-	2
484	H		iPr-	H	-Me	-CONH-	2

Table 1 (continued)

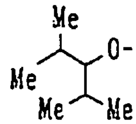
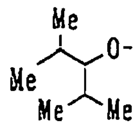
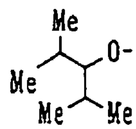
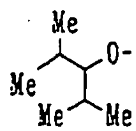
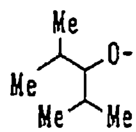
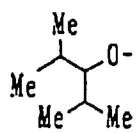
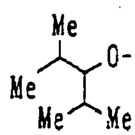
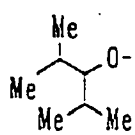
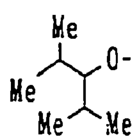
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
485	H		Me-O-	H	-Me	-CONH-	2
486	H		Et-O-	H	-Me	-CONH-	2
487	H		iPr-O-	H	-Me	-CONH-	2
488	-OH		H	H	-Me	-CONH-	2
489	-Me		H	H	-Me	-CONH-	2
490	-F		H	H	-Me	-CONH-	2
491	-Cl		H	H	-Me	-CONH-	2
492	-Br		H	H	-Me	-CONH-	2
493	H		H	F-	-Me	-CONH-	2

Table 1 (continued)

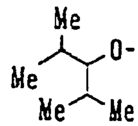
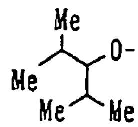
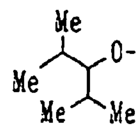
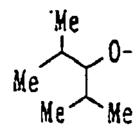
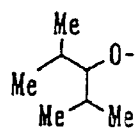
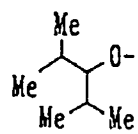
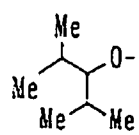
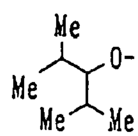
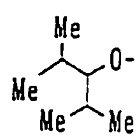
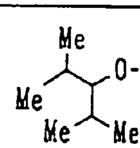
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
494	H		H	Cl-	-Me	-CONH-	2
495	H		H	Br-	-Me	-CONH-	2
496	H		H		-Me	-CONH-	2
497	H		H	H	-Me	-CONMe-	2
498	H		Me-	H	-Me	-CONMe-	2
499	H		Et-	H	-Me	-CONMe-	2
500	H		iPr-	H	-Me	-CONMe-	2
501	H		Me-O-	H	-Me	-CONMe-	2
502	H		Et-O-	H	-Me	-CONMe-	2

Table 1 (continued)

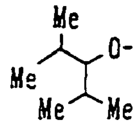
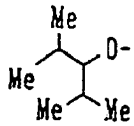
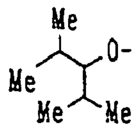
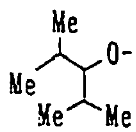
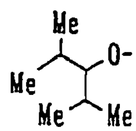
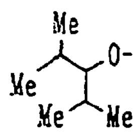
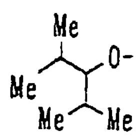
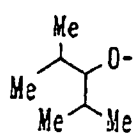
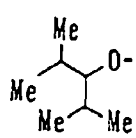
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
503	H		iPr-O-	H	-Me	-CONMe-	2
504	-OH		H	H	-Me	-CONMe-	2
505	H		H	H	-Me	-CONH-	1
506	H		Me-	H	-Me	-CONH-	1
507	H		Et-	H	-Me	-CONH-	1
508	H		iPr-	H	-Me	-CONH-	1
509	H		Me-O-	H	-Me	-CONH-	1
510	H		Et-O-	H	-Me	-CONH-	1
511	H		iPr-O-	H	-Me	-CONH-	1

Table 1 (continued)

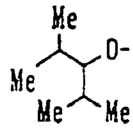
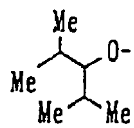
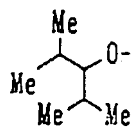
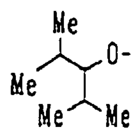
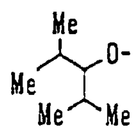
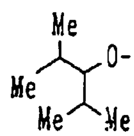
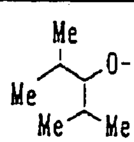
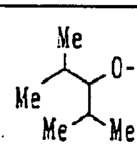
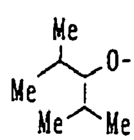
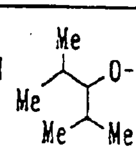
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
512	-OH		H	H	-Me	-CONH-	1
513	-Me		H	H	-Me	-CONH-	1
514	-F		H	H	-Me	-CONH-	1
515	-Cl		H	H	-Me	-CONH-	1
516	-Br		H	H	-Me	-CONH-	1
517	H		H	F-	-Me	-CONH-	1
518	H		H	Cl-	-Me	-CONH-	1
519	H		H	Br-	-Me	-CONH-	1
520	H		H		-Me	-CONH-	1

Table 1 (continued)

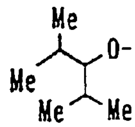
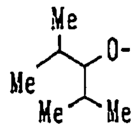
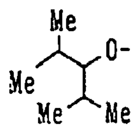
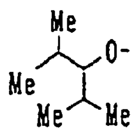
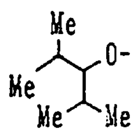
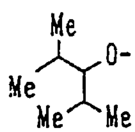
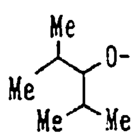
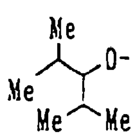
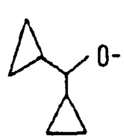
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
521	H		H	H	-Me	-CONMe-	1
522	H		Me-	H	-Me	-CONMe-	1
523	H		Et-	H	-Me	-CONMe-	1
524	H		iPr-	H	-Me	-CONMe-	1
525	H		Me-O-	H	-Me	-CONMe-	1
526	H		Et-O-	H	-Me	-CONMe-	1
527	H		iPr-O-	H	-Me	-CONMe-	1
528	-OH		H	H	-Me	-CONMe-	1
529	H		H	H	-Me	-CONH-	2

Table 1 (continued)

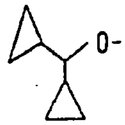
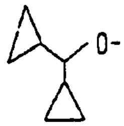
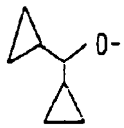
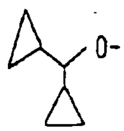
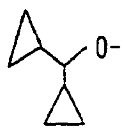
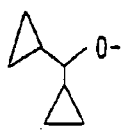
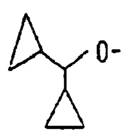
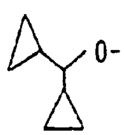
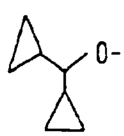
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
530	H		Me-	H	-Me	-CONH-	2
531	H		Et-	H	-Me	-CONH-	2
532	H		iPr-	H	-Me	-CONH-	2
533	H		Me-O-	H	-Me	-CONH-	2
534	H		Et-O-	H	-Me	-CONH-	2
535	H		iPr-O-	H	-Me	-CONH-	2
536	-OH		H	H	-Me	-CONH-	2
537	-Me		H	H	-Me	-CONH-	2
538	-F		H	H	-Me	-CONH-	2

Table 1 (continued)

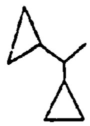
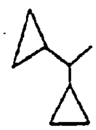
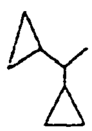
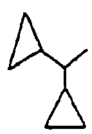
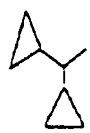
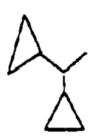
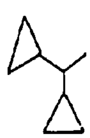
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
539	-Cl	 O-	H	H	-Me	-CONH-	2
540	-Br	 O-	H	H	-Me	-CONH-	2
541	H	 O-	H	F-	-Me	-CONH-	2
542	H	 O-	H	Cl-	-Me	-CONH-	2
543	H	 O-	H	Br-	-Me	-CONH-	2
544	H	 O-	H	 O-	-Me	-CONH-	2
545	H	 O-	H	H	-Me	-CONMe-	2
546	H	 O-	Me-	H	-Me	-CONMe-	2
547	H	 O-	Et-	H	-Me	-CONMe-	2

Table 1 (continued)

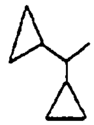
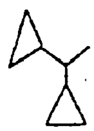
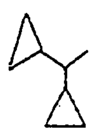
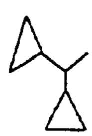
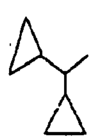
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
548	H	 O-	iPr-	H	-Me	-CONMe-	2
549	H	 O-	Me-O-	H	-Me	-CONMe-	2
550	H	 O-	Et-O-	H	-Me	-CONMe-	2
551	H	 O-	iPr-O-	H	-Me	-CONMe-	2
552	-OH	 O-	H	H	-Me	-CONMe-	2
553	H	 O-	H	H	-Me	-CONH-	1
554	H	 O-	Me-	H	-Me	-CONH-	1
555	H	 O-	Et-	H	-Me	-CONH-	1
556	H	 O-	iPr-	H	-Me	-CONH-	1

Table 1 (continued)

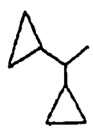
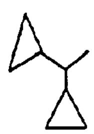
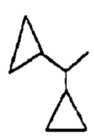
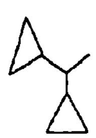
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
557	H	 O-	Me-O-	H	-Me	-CONH-	1
558	H	 O-	Et-O-	H	-Me	-CONH-	1
559	H	 O-	iPr-O-	H	-Me	-CONH-	1
560	-OH	 O-	H	H	-Me	-CONH-	1
561	-Me	 O-	H	H	-Me	-CONH-	1
562	-F	 O-	H	H	-Me	-CONH-	1
563	-Cl	 O-	H	H	-Me	-CONH-	1
564	-Br	 O-	H	H	-Me	-CONH-	1
565	H	 O-	H	F-	-Me	-CONH-	1

Table 1 (continued)

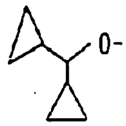
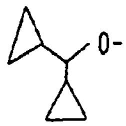
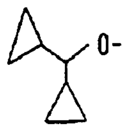
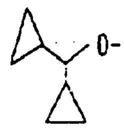
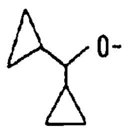
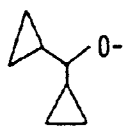
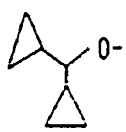
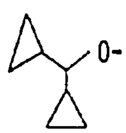
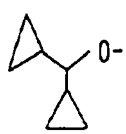
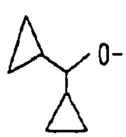
Compd. No.	R¹	R²	R³	R⁴	R⁵	X	n
566	H		H	Cl-	-Me	-CONH-	1
567	H		H	Br-	-Me	-CONH-	1
568	H		H		-Me	-CONH-	1
569	H		H	H	-Me	-CONMe-	1
570	H		Me-	H	-Me	-CONMe-	1
571	H		Et-	H	-Me	-CONMe-	1
572	H		iPr-	H	-Me	-CONMe-	1
573	H		Me-O-	H	-Me	-CONMe-	1
574	H		Et-O-	H	-Me	-CONMe-	1

Table 1 (continued)

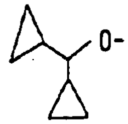
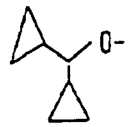
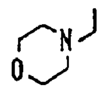
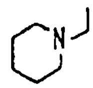
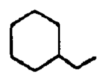
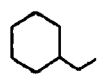
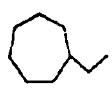
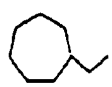
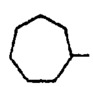
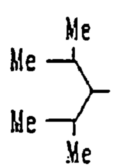
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
575	H		iPr-O-	H	-Me	-CONMe-	1
576	-OH		H	H	-Me	-CONMe-	1
577	H		H	H	-Me	-CONH-	2
578	H		H	H	-Me	-CONH-	2
579	H		H	H	-Me	-CONH-	2
580	H		H	H	-Me	-CONH-	1
581	H		H	H	-Me	-CONH-	2
582	H		H	H	-Me	-CONH-	1
583	H		H	H	-Me	-CONH-	2
584	H		H	H	-Me	-CONH-	2

Table 1 (continued)

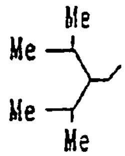
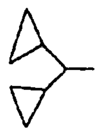
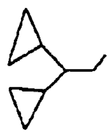
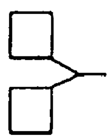
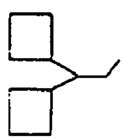
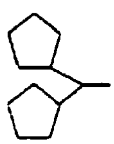
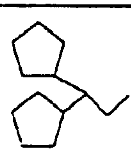
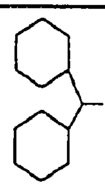
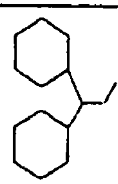
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
585	H		H	H	-Me	-CONH-	2
586	H		H	H	-Me	-CONH-	2
587	H		H	H	-Me	-CONH-	2
588	H		H	H	-Me	-CONH-	2
589	H		H	H	-Me	-CONH-	2
590	H		H	H	-Me	-CONH-	2
591	H		H	H	-Me	-CONH-	2
592	H		H	H	-Me	-CONH-	2
593	H		H	H	-Me	-CONH-	2

Table 1 (continued)

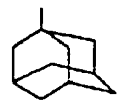
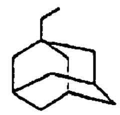
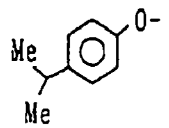
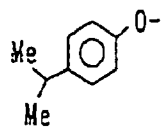
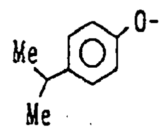
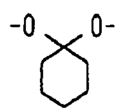
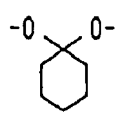
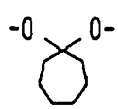
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
594	H		H	H	-Me	-CONH-	2
595	H		H	H	-Me	-CONH-	2
596	H		H	Br-	-Me	-CONH-	2
597	H		H		-Me	-CONH-	2
598	H	$-OCH_2O-$		H	-Me	-CONH-	2
599	H	$-OCH_2O-$		H	-Me	-CONH-	1
600	H	$-OCH_2CH_2O-$		H	-Me	-CONH-	2
601	H	$-OCH_2CH_2O-$		H	-Me	-CONH-	1
602	H			H	-Me	-CONH-	2
603	H			H	-Me	-CONH-	1
604	H			H	-Me	-CONH-	2

Table 1 (continued)

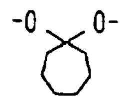
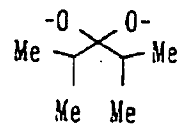
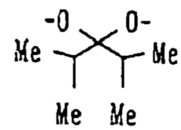
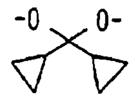
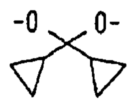
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
605	H			H	-Me	-CONH-	1
606	H			H	-Me	-CONH-	2
607	H			H	-Me	-CONH-	1
608	H			H	-Me	-CONH-	2
609	H			H	-Me	-CONH-	1
610	H	t-Bu-	H	t-Bu-	-Me	-CONH-	2
611	H	t-Bu-	H	t-Bu-	-Me	-CONMe-	2
612	H	t-Bu-	H	t-Bu-	-Me	-CONH-	1
613	H	t-Bu-	H	t-Bu-	-Me	-CONMe-	1
614	H	iPr-	H	iPr-	-Me	-CONH-	2
615	H	iPr-	H	iPr-	-Me	-CONH-	1

Table 1 (continued)

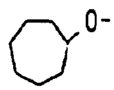
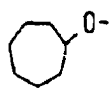
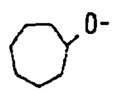
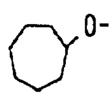
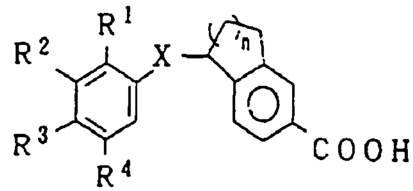
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
616	H	$-C(CH_3)_2CH_2CH_2C(CH_3)_2-$		H	-Me	-CONH-	2
617	H	$-C(CH_3)_2CH_2CH_2C(CH_3)_2-$		H	-Me	-CONH-	1
618	H	$-C(CH_3)_2CH_2CH_2C(CH_3)_2-$		H	-Me	-CONMe-	2
619	H	$-C(CH_3)_2CH_2CH_2C(CH_3)_2-$		H	-Me	-CONEt-	2
620	H		H	H	-Me	$-SO_2NH-$	2
621	H		H	H	-Me	$-SO_2NH-$	1
622	H		H	H	-Me	$-SO_2NMe-$	2
623	H		H	H	-Me	$-SO_2NEt-$	2

Table 2



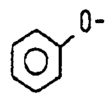
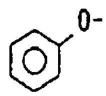
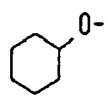
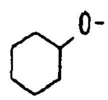
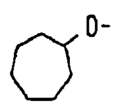
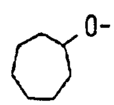
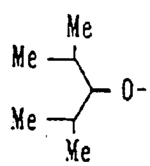
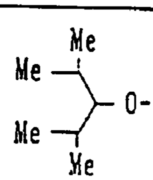
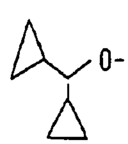
Compd. No.	R^1	R^2	R^3	R^4	X	n
624	H		H	H	-CONH-	2
625	H		H	H	-CONH-	1
626	H		H	H	-CONH-	2
627	H		H	H	-CONH-	1
628	H		H	H	-CONH-	2
629	H		H	H	-CONH-	1
630	H		H	H	-CONH-	2
631	H		H	H	-CONH-	1
632	H		H	H	-CONH-	2

Table 2 (continued)

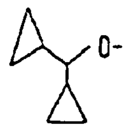
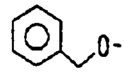
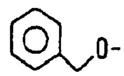
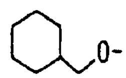
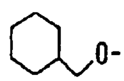
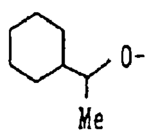
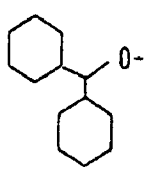
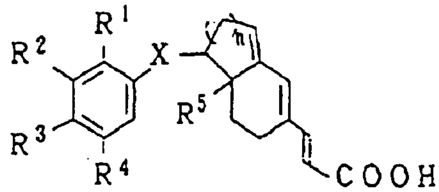
Compd. No.	R¹	R²	R³	R⁴	X	n
633	H		H	H	-CONH-	1
634	H		H	H	-CONH-	2
635	H		H	H	-CONH-	1
636	H		H	H	-CONH-	2
637	H		H	H	-CONH-	1
638	H		H	H	-CONH-	2
639	H		H	H	-CONH-	2

Table 3



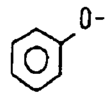
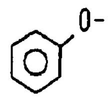
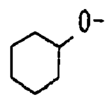
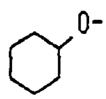
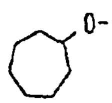
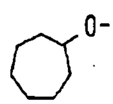
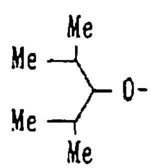
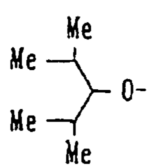
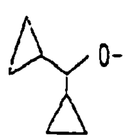
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
640	H		H	H	-Me	-CONH-	2
641	H		H	H	-Me	-CONH-	1
642	H		H	H	-Me	-CONH-	2
643	H		H	H	-Me	-CONH-	1
644	H		H	H	-Me	-CONH-	2
645	H		H	H	-Me	-CONH-	1
646	H		H	H	-Me	-CONH-	2
647	H		H	H	-Me	-CONH-	1
648	H		H	H	-Me	-CONH-	2

Table 3 (continued)

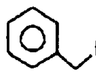
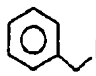
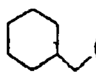
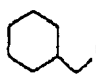
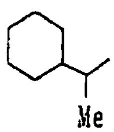
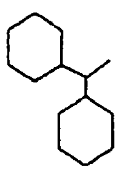
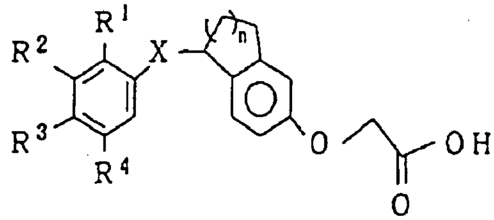
Compd. No.	R^1	R^2	R^3	R^4	R^5	X	n
649	H	 O-	H	H	-Me	-CONH-	1
650	H	 O-	H	H	-Me	-CONH-	2
651	H	 O-	H	H	-Me	-CONH-	1
652	H	 O-	H	H	-Me	-CONH-	2
653	H	 O-	H	H	-Me	-CONH-	1
654	H	 O-	H	H	-Me	-CONH-	2
655	H	 O-	H	H	-Me	-CONH-	2

Table 4



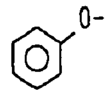
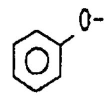
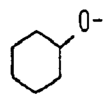
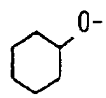
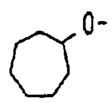
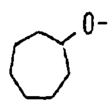
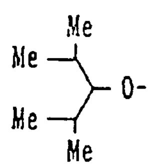
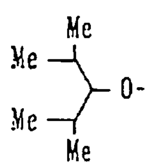
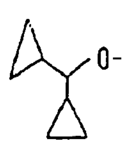
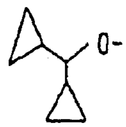
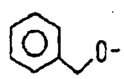
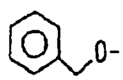
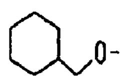
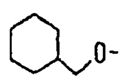
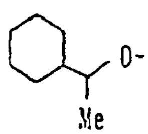
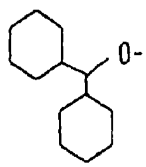
Compd. No.	R^1	R^2	R^3	R^4	X	n
656	H		H	H	-CONH-	2
657	H		H	H	-CONH-	1
658	H		H	H	-CONH-	2
659	H		H	H	-CONH-	1
660	H		H	H	-CONH-	2
661	H		H	H	-CONH-	1
662	H		H	H	-CONH-	2
663	H		H	H	-CONH-	1
664	H		H	H	-CONH-	2

Table 4 (continued)

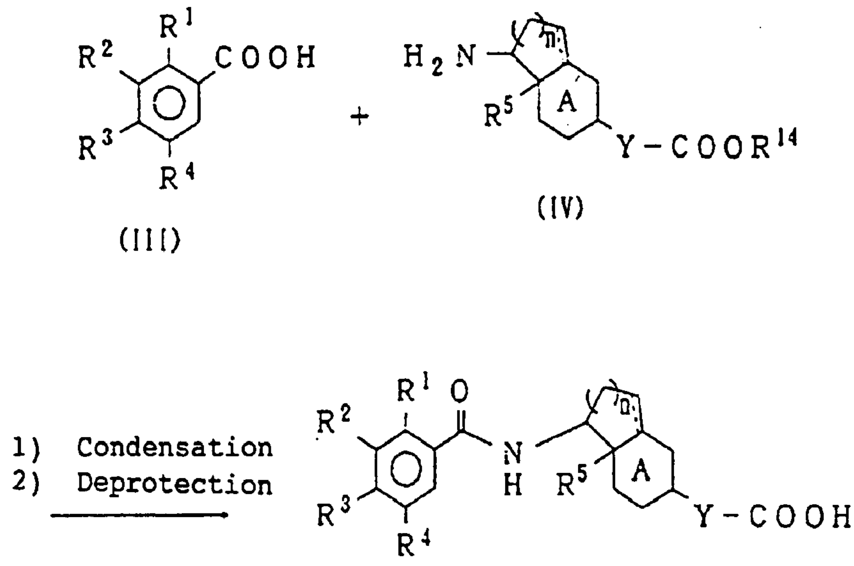
Compd. No.	R^1	R^2	R^3	R^4	X	n
665	H		H	H	-CONH-	1
666	H		H	H	-CONH-	2
667	H		H	H	-CONH-	1
668	H		H	H	-CONH-	2
669	H		H	H	-CONH-	1
670	H		H	H	-CONH-	2
671	H		H	H	-CONH-	2

In Tables 1 - 4, Me means a methyl group, Et means an ethyl group, Pr means a propyl group, iPr means an isopropyl group, Bu means a butyl group, and Ac means an acetyl group.

The compounds of the general formula (I) can form a salt with a base. The base may be selected from those which can form a salt with the compound of the general formula (I). Examples of the salts are metal salts (e.g. sodium salt, magnesium, aluminium salt, etc.), ammonium salt, and amine salts (e.g. methylamine, ethylamine, diethylamine, triethylamine, pyrolidine, piperidine, morpholine, pyridine, aniline, etc.).

The compounds of the general formula (I) can be prepared, for example, in the manner as shown in the following synthetic route.

(1) Of the compounds of the general formula (I), the compounds wherein X is $-CONR^{13}-$ are prepared as follows:

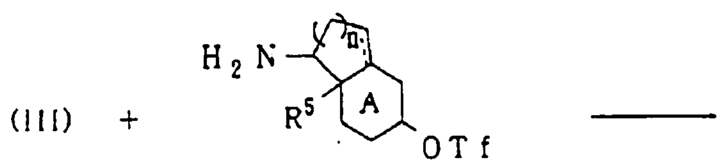


(Ia)

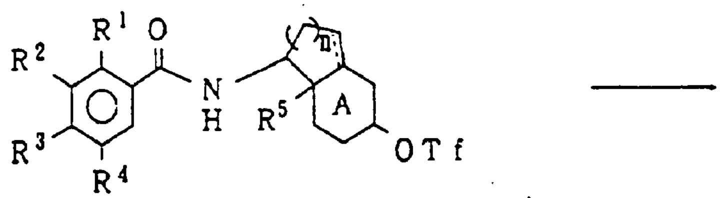
In the above formulae, R^1, R^2, R^3, R^4, R^5, n, Y and A have the same significance as defined in the general formula (I) above, and R^{14} represents an alkyl group having 1 to 5 carbon atoms.

For example, the benzoic acid derivatives of the general formula (III) is allowed to condense with amino acid derivatives of the general formula (IV) in an appropriate solvent such as methylene chloride, chloroform, tetrahydrofuran, benzene or the like, or without solvent, in the presence or absence of a condensing agent and an organic base, or in the presence of a condensing agent without base. The condensing agent includes inorganic condensing agents such as phosphorus oxychloride, thionyl chloride or the like and organic condensing agents such as dicyclohexylcarbodi-imide, carbodiimidazole, oxalyl chloride, tosyl chloride or the like. The condensed product is subjected to hydrolysis with an alkali to give the objective compound (Ia). The hydrolysis is carried out in a mixture of water and methanol containing an alkali metal hydroxide such as sodium hydroxide or the like, or in a mixture of water, methanol and tetrahydrofuran.

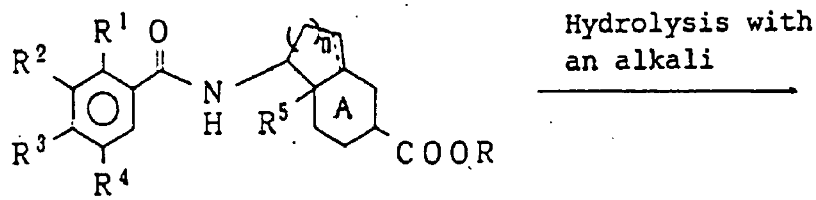
The compound of the general formula (I) in which Y is a single bond can be prepared, for example, by condensing the compound of the general formula (III) with the amine derivative of the general formula (V) below using the method mentioned above, to give the compound of the general formula (VI) below, and this compound is allowed to react with carbon monoxide in the presence of an organic base, phosphine and palladium (II) in an alkanol (ROH) solvent or in a mixture of alkanol (ROH) of 1 -5 carbon atoms with tetrahydrofuran, ether, methylene chloride or the like, to give alkoxycarbonyl compound of the general formula (VII) below, which is then subjected to hydrolysis with an alkali to give the objective compound. (The alkali-hydrolysis is carried out as described above.)



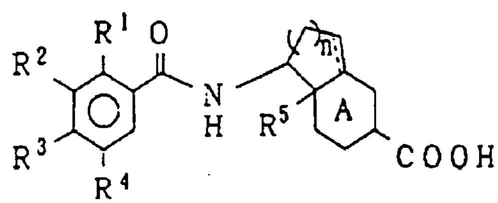
(V)



(VI)



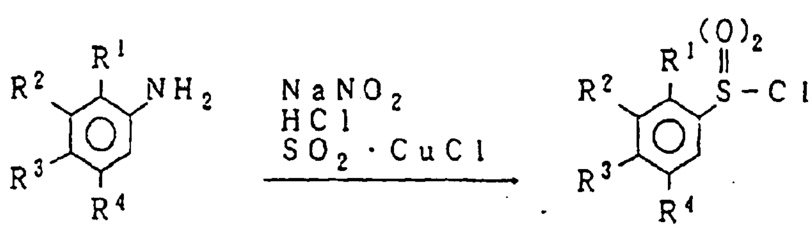
(VII)



(VIII)

In the above formulae, R^1, R^2, R^3, R^4, R^5, n and A have the same significance as defined above, R represents an alkyl group of 1 to 5 alkyl group, and Tf represents trifluoro-methanesulfonyl group.

(2) Production of the compound of the general formula (I) in which X is $-SO_2NR^{13}-$

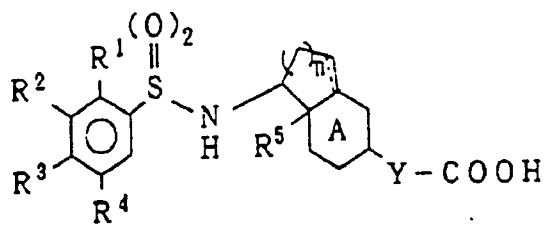


(IX) (X)

In the above formulae, R^1, R^2, R^3 and R^4 have the same significance as defined above.

For example, the aniline derivative of the general formula (IX) above is allowed to react with sodium nitrite or potassium nitrite in an appropriate solvent such as aqueous acetic acid, diluted hydrochloric acid or the like, to give a diazonium salt, which is allowed to react with cupric chloride and sulfur dioxide to give the sulfonyl chloride derivative of the general formula (X) above.

The compound of the general formula (XI) below can be prepared by reacting the compound of the general formula (X) with the compound of the general formula (IV) above in the presence or absence of an organic base such as triethylamine, pyridine or the like, in a halogen type solvent such as methylene chloride or the like and subjecting the resultant product to alkali-hydrolysis according to the method as described above.



(XI)

In the above formulae (XI), R^1, R^2, R^3, R^4, R^5, n, Y and A have the same significance as defined in the general formula (I).

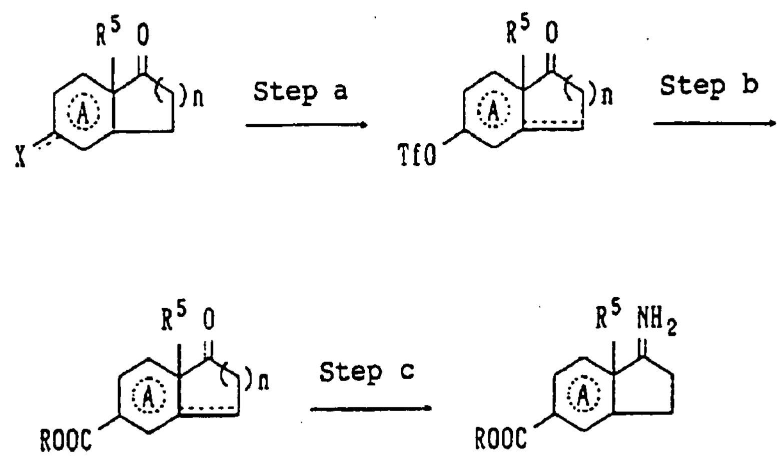
(3) Production of amino acid derivatives of the general formula (IV):

i) Production of compounds of the general formula (IV) in which Y is a single bond or -CH=CH-:

The starting 8a-methyl-3,4,8,8a-tetrahydro-1,6(2H,7H)-naphthalenedione and 7a-methyl-7,7a-tetrahydro-1,5(6H)-indadione are known compounds, and their optical activity is also known. Furthermore, the starting 6-hydrotetralone and 5-hydroxyindanone are known compounds.

The starting compounds are treated at temperature from -40°C to room temperature in the presence of 1 mol equivalent of anhydrous trifluoromethanesulfonic acid and tertiary amine such as triethylamine, pyridine or the like, in an inert solvent such as methylene chloride, tetrahydrofuran or the like (Step a), and the resultant product is allowed to react with carbon monoxide or the like in the presence of an organic base, phosphine and palladium (II) in a mixture of alcohol (1 - 5 carbon atoms) with tetrahydrofuran or ether to give an alkoxy compound (Step b). This product is treated with a reducing agent such as sodium cyanoborohydride or the like in the presence of ammonium salt such as ammonium acetate, ammonium chloride or the like, in an alkanol solvent (1 - 5 carbon atoms) or in a mixture of alkanol (1 - 5 carbon atoms) with tetrahydrofuran or ether for subjecting only the ketone group to reductive amination (Step c).

The compound wherein Y is -CH=CH- can be prepared by using an alkyl acrylate or the like in place of carbon monoxide in Step b.



In the above formulae, R^5, X, n and A have the same significance as defined in the general formula (I), and R represents an alkyl group having 1 - 5 carbon atoms.

ii) Production of the compound of the general formula (IV) in which Y is $-OCH_2-$:

For example, 6-hydroxytetralone or 5-hydroxyindanone is allowed to react with α-haloacetic acid ester in the presence of a base such as sodium hydride, triethylamine or the like in a solvent such as methylene chloride, tetrahydrofuran, DMF or the like, and the resultant product is subjected to reductive animation to give the product.

The benzoic acid derivative of the formula (III) and aniline derivative of the formula (IX) are commercially available or can be prepared in a conventional manner from commercially available materials.

When the compounds of the present invention are used as medicaments, they can be formulated together with one or more of conventional carriers suitable for desired administering route. For example, formulations such as tablets, capsules, granules, powders, solutions or the like are prepared for oral route. Excipients, binders, lubricants, coloring agents, disintegrators, or the like, which are usually employed for the preparation of pharmaceutical formulations, can be used for preparing solid formulations for oral route. Examples of the excipients are lactose, starch, talc, magnesium stearate, crystalline cellulose, methyl cellulose, carboxymethyl cellulose, glycerin, sodium alginate, arabic gum and the like. Examples of the binders are polyvinyl alcohol, polyvinyl ether, ethyl cellulose, arabic gum, shellac, refined sugar and the like. Examples of the lubricants are magnesium stearate, talc, and the like. Additionally, coloring agents and disintegrators may be used. Further, tablets may be coated in a conventional manner. Liquid formulations include aqueous or oily suspensions, solutions, syrups, elixils and the like, and can be prepared in a conventional manner. Injections may be prepared by adding pH adjusting agents, buffers, stabilizers, isotonic agents, topical anesthetics, or the like to the compound of the present invention. Subcutaneous, intramuscular or intravenous injections may be prepared in a conventional manner. For preparing suppositories, oily bases such as cacao oil, polyethylene glycol, Witepsol (Trademark of Dynamite Novel Company) or the like may be used.

Appropriate dosage of the formulation thus obtained varies depending upon symptoms, body weight, age or the like of particular patients. In general, appropriate daily dose to adult is in the range from about 0.01 to 2000 mg, and the daily dose is preferably administered in multiple doses of 1 - 4 times a day.

Appropriate salts of the compound (I) may be prepared using a non-toxic base. Such appropriate salts include those formed with inorganic bases (e.g. sodium slat, potassium salt, etc.), those formed with organic bases (e.g. triethylamine, etc.), and ammonium salts.

EXAMPLES

The present invention will be explained in more detail below by examples and reference examples. The examples are representative only and should not be construed as limiting in any respect.

Example 1

Preparation of 5-(4'-phenoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 1 in Table 1):

To a solution of 4-phenoxybenzoic acid (410 mg, 1.91 mmol) in methylene chloride (4.0 ml) was added thionyl chloride (0.8 ml), and the resultant mixture was refluxed for 1 hour. The mixture was concentrated, and the residue was dissolved in methylene chloride (4.0 ml) and the resulting solution was dropwise added to a solution of 5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (420 mg, 1.92 mmol), triethylamine (0.84 ml) and methylene chloride (4.2 ml) under ice cooling. The mixture was stirred at room temperature for 30 minutes, poured into chilled water (50 ml) and extracted with ethyl acetate. The organic extract was concentrated to dryness, and the residue was dissolved in 10% methanolic water (23 ml), mixed with potassium hydroxide (1.09 g, 16.5 mmol) and refluxed for 4 hours. The product was extracted with acidic chloroform, dried over magnesium sulfate and concentrated. The resulting residue was chromatographed on a silica gel column, eluting with chloroform-methanol to give the titled compound (464 mg, yield 60%) as white crystals.

m.p.96-101°C

^{1}H-NMR($CDCl_3$, 250MHz)δppm=7.73(d, 2H, 8.7Hz), 7.36(t-like, 2H, 7.4Hz), 7.1-7.2(m, 2H), 6.9-7.1(m, 4H), 5.96 (br-d, 1H, 8.7Hz), 5.90(br-s, 1H), 4.10-4.25(m, 1H), 4.10-4.25(m, 1H), 2.10-2.60(m, 4H), 1.75-1.95(m, 3H), 1.40-1.55(m, 1H), 1.01(s, 1H)

IR(KBr):ν(cm^{-1})=3296, 2938, 1674, 1634, 1588, 1543, 1489, 1244, 1169.

Example 2

Preparation of 5-(3'-phenoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 10 in Table 1):

The reaction was effected with 3-phenoxybenzoic acid (542 mg, 2.53 mmol) in the same manner as in Example 1 to give the titled compound (412 mg, yield 40%).

m.p.181-186°C

^{1}H-NMR(CDCl$_3$, 250MHz)δ(ppm)=7.33-7.49(m, 5H), 7.10-7.20 (m, 5H), 5.98(d, 1H, J=9.7Hz), 5.91(t, 1H, J=3.7Hz), 4.13-4.26(m, 1H), 2.14-2.59(m, 3H), 1.82-1.92(m, 4H), 1.40-1.53(m, 1H), 1.02(s, 3H)

IR(KBr):ν(cm^{-1})=3285, 3069, 9240, 1672, 1634, 1580, 1555, 1483, 1427, 1306, 1275, 1233.

Example 3

Preparation of 5-(2'-phenoxybenzoylamino)-10-methyl-Δ$^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 12 in Table 1):

The reaction was effected with 2-phenoxybenzoic acid (488 mg, 2.28 mmol) as in the same manner as in Example 1 to give the titled compound (330 mg, yield 36%).

m.p.75-77°C

^{1}H-NMR(CDCl$_3$, 250MHz)δ=8.23(dd, 1H, 1.8Hz, 7.9Hz), 7.73(br-d, 1H, 8.0Hz), 7.3-7.42(m, 3H), 7.1-7.3(m, 3H), 7.00(d, 2H, 7.9Hz), 6.87(d, 1H, 8.2Hz), 5.85(br-s, 1H), 4.1-4.2(m, 1H), 2.2-2.5(m, 3H), 2.0-2.2(m, 1H), 1.8-1.9(m, 1H), 1.6-1.8(m, 2H), 1.2-1.4(m, 1H), 0.84(s, 3H)

IR(KBr):ν(cm^{-1})=3403, 3069, 2932, 1640, 1601, 1534, 1478, 1449, 1223, 753.

Example 4

Preparation of 5-[3'-(p-isopropylphenoxy)benzoylamino]-10-methyl-Δ$^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 16 in Table 1):

The reaction was effected with 3-(p-isopropylphenoxy)benzoic acid (177 mg, 0.74 mmol) in the same manner as in Example 1 to give the titled compound (253 mg, yield 77%). m.p.146-149°C

^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.3-7.45(m, 3H), 7.15-7.23(m, 3H), 7.10(dd, 1.4Hz, 8.0Hz), 6.90-6.96(m, 2H), 5.98 (br-d, 1H, 8.7Hz), 5.90(br-s, 1H), 4.1-4.2(m, 1H), 2.80-2.95(m, 1H), 2.10-2.60(m, 4H)1.70-1.95(m, 3H), 1.35-1.50 (m, 1H), 1.22, 1.25(each s, each 3H), 0.99(s, 3H)

IR(KBr):ν(cm^{-1})=3312, 2959, 2930, 2870, 1674, 1636, 1582, 1541, 1507, 1480, 1429, 1306, 1279, 1236.

Example 5

Preparation of 5-[3'-(m-isopropylphenoxy)benzoylamino]-10-methyl-Δ$^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 17 in Table 1):

The reaction was effected with 3-(m-isopropylphenoxy)benzoic acid (704 mg, 2.75 mmol) in the same manner as in Example 1 to give the titled compound (612 mg, yield 50%).

m.p.83-86°C

^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.3-7.47(m, 3H), 7.25(dd, 1H, 7.9Hz, 7.8Hz), 7.17(br-s, 1H), 7.10(ddd, 1.3Hz, 2.2Hz, 7.9Hz), 7.00(br-d, 1H, 7.8Hz), 6.90(dd, 1H, 2.1Hz, 1.8Hz), 6.79(ddd, 1H, 0.8Hz, 2.2Hz, 7.9Hz), 5.95(d, 1H, 9.7Hz), 5.90(dd, 1H, 3.8Hz, 3.7Hz), 4.11-4.23 (m, 1H), 2.87(dq, 1H, each 6.9Hz), 2.52(dd, 1H, 4.7Hz, 19Hz), 2.10- 2.47 (m, 3H), 1.76-1.90(m, 3H), 1.37-1.49(m, 1H), 1.22(d, 6H, 6.9Hz), 1.02(s, 3H)

IR(KBr):ν(cm^{-1})=3285, 3071, 2961, 2870, 2822, 1672, 1634, 1576, 1555, 1481, 1427, 1308, 1273, 1244.

Example 6

Preparation of 5-[3'-(o-isopropylphenoxy)benzoylamino]-10-methyl-Δ$^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 18 in Table 1):

The reaction was effected with 3-(o-isopropylphenoxy)benzoic acid (347 mg, 1.44 mmol) in the same manner as in Example 1 to give the titled compound (344 mg, yield 54%).

m.p.192-194°C

^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.3-7.4(m, 4H), 7.1-7.2(m, 2H), 6.98(dd-like, 1H, 1.4Hz, 8.0Hz), 6.80-6.90(m, 1H), 5.98(br-d, 1H, 8.7Hz), 5.90(br-s, 1H), 4.1-4.25(m, 1H), 3.1-3.3(m, 1H), 2.1-2.6 (m, 4H), 1.7-1.9(m, 3H), 1.3-1.5(m, 1H), 1.21, 1.19(each s, each 3H), 0.99(s, 3H)

IR(KBr):ν(cm^{-1})=3291, 3071, 2961, 2870, 2824, 2629, 1674, 1634, 1578, 1555, 1483, 1451, 1429, 1306, 1275, 1235, 1184.

Example 7

Preparation of 5-[3'-(p-tolyloxy)benzoylamino]-10-methyl-$\Delta^{1(2), 8(9)}$-octalin-2-carboxylic acid (Compound No. 21 in Table 1):

To a mixture of 3-(p-tolyloxy)benzoic acid (414 mg, 1.81 mmol), 5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (401 mg, 1.81 mmol), triethylamine (1.26 mg, 9.05 mmol) and methylene chloride (4.1 ml) was added thionyl chloride (396 µl, 5.43 mmol) with ice cooling. The resultant mixture was stirred at room temperature for 30 minutes, poured into chilled water (50 ml), and extracted with ethyl acetate. The organic extract was concentrated, and the residue was dissolved in a mixture of 10% methanol (12 ml) and THF (3.7 ml), mixed with potassium hydroxide (566 mg, 8.57 mmol) and refluxed for 3 hours. The product was extracted with acidic chloroform, and the organic layer was dried and concentrated. The resultant residue was chromatographed on a silica gel column, eluting with chloroform-methanol to give the titled compound (263 mg, yield 35%).

m.p.168-172°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.3-7.4(m, 3H), 7.0-7.2(m, 4H), 6.90 (d, 2H, 8.5Hz), 6.00(d, 1H, 9.6Hz), 5.89(br-s, 1H), 4.1-4.2(m, 1H), 2.1-2.6(m, 4H), 2.32(s, 3H), 1.7-1.9(m, 3H), 1.40(ddd, 1H, 5.7Hz, 5.7Hz, 13Hz), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3283, 2940, 1672, 1634, 1580, 1559, 1507, 1481, 1427, 1306, 1275, 1238, 1209, 1186.

Example 8

Preparation of 5-[3'-(p-t-butylphenoxy)benzoylamino]-10-methy-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 24 in Table 1):

The reaction was effected with 3-(p-t-butylphenoxy)benzoic acid (435 mg, 1.61 mmol) in the same manner as in Example 7 to give the titled compound (282 mg, yield 38%).

m.p.233-238°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.3-7.45(m, 5H), 7.16(d, 1H, 1.5Hz), 7.52(dd-like, 1H, 1Hz, 1.5Hz, 8.0Hz), 6.94(d, 2H, 8.9Hz), 5.96 (br-d, 1H, 8.7Hz), 5.86(br-s, 1H), 4.05-4.20(m, 1H), 2.10-2.60(m, 4H), 1.75-1.95(m, 3H), 1.40-1.55 (m, 1H), 1.30(s, 9H), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3266, 2965, 2870, 1680, 1634, 1613, 1580, 1543, 1508, 1480, 1426, 1306, 1279, 1236.

Example 9

Preparation of 5-{3"-[p-(2'-methylpropyl]phenoxy)benzoylamino}-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 30 in Table 1):

The reaction was effected with 3-p-(2'-methylpropyl)phenoxybenzoic acid (246 mg, 0.91 mmol) in the same manner as in Example 7 to give the titled compound (290 mg, yield 69%).

m.p.142-148°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.3-7.45(m, 3H), 7.18(s-like, 1H), 7.06-7.13(m, 3H), 6.92(d, 2H, 11.3Hz), 5.95(d, 1H, 9.7Hz), 5.90 (br-s, 1H), 4.10-4.22(m, 1H), 4.52(dd, 1H, 4.1Hz, 18.3Hz), 2.44(d, 2H, 7.2Hz), 2.15-4.60(m, 3H), 1.75-1.95(m, 4H), 1.42(ddd, 1H, 5.7Hz, 5.7Hz, and 13Hz), 0.99(s, 3H), 0.89(d, 6H, 6.5Hz)
IR(KBr):ν(cm^{-1})=3289, 2959, 2870, 1672, 1638, 1609, 1584, 1545, 1505, 1481, 1431, 1308, 1279, 1235.

Example 10

Preparation of 5-[3'-(p-cyclopentylphenoxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 33 in Table 1):

The reaction was effected with 3-(p-cyclopenthylphenoxy)benzoic acid (488 mg, 1.73 mmol) in the same manner as in Example 7 to give the titled compound (240 mg, yield 30%).

m.p.229-231°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.3-7.4(m, 3H), 7.15-7.25(m, 3H), 7.09(ddd, 1H, 1.4Hz, 0, 8Hz, 9.2Hz), 6.93(d, 2H, 8.5Hz), 5.96(d, 1H, 9.6Hz), 5.89(br-s, 1H), 4.05-4.20(m, 1H), 2.85-3.05(m, 1H), 1.95-2.30(m, 6H), 1.30-1.90(m, 10H), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3337, 2944, 2868, 1676, 1638, 1613, 1578, 1543, 1505, 1483, 1426, 1323, 1304, 1275, 1236.

Example 11

Preparation of 5-[3'-(p-cyclohexylphenoxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 36 in Table 1):

The reaction was effected with 3-(p-cyclohexylphenoxy)benzoic acid (415 mg, 1.40 mmol) in the same manner as in Example 7 to give the titled compound (263 mg, yield 33%).

m.p.124-125°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.3-7.45(m, 3H), 7.1-7.2(m, 3H), 7.10(ddd, 1H, 1.3Hz, 2.4Hz, 7.9Hz), 6.92(d, 2H, 8.5Hz), 5.97(br-d, 1H, 9.5Hz), 5.89(br-s, 1H), 4.10-4.25(m, 1H), 2.10-2.60(m, 5H), 1.65-1.95(m, 8H), 1.10-1.50(m, 6H), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3443, 2926, 2851, 1676, 1636, 1580, 1541, 1507, 1480, 1429, 1306, 1273, 1238.

Example 12

Preparation of 5-[3'-(p-N-methylaminocarbonylphenoxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 38 in Table 1):

The reaction was effected with 3-(p-N-methyl-amino-carbonylphenoxy)benzoic acid (448 mg, 1.19 mmol) in the same manner as in Example 7 to give the titled compound (35 mg, yield 6.4%).

m.p.123-127°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.72(d, 2H, 8.6Hz), 7.35-7.55(m, 3H), 7.10-7.20(m, 2H), 6.97(d, 2H, 8.6Hz), 6.30(br-d-like), 6.10(br-d, 1H, 9.5Hz), 5.87(br-s, 1H), 2.96, 2.98(each s, total 3H), 2.1-2.6 (m, 4H), 1.6-1.9(m, 3H), 1.3-1.5 (m, 1H), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3337, 3069, 2936, 1684, 1636, 1578, 1543, 1501, 1316, 1240, 1177.

Example 13

Preparation of 5-[3'-(2, 4-dimethylphenoxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 42 in Table 1):

The reaction was effected with 3-(2',4'-dimethylphenoxy) benzoic acid (271 mg, 1.12 mmol) in the same manner as in Example 7 to give the titled compound (135 mg, yield 28%).

m.p.137-142°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.3-7.45(m, 3H), 7.18(d, 1H, 2.0Hz), 7.09(ddd, 1H, 1.2Hz, 2.2Hz, 9.0Hz), 6.76(d, 1H, 0.6Hz), 6.62(d, 2H, 0.6Hz), 5.97(br-d, 1H, 9.6Hz), 5.89(dd, 1H, each 3.7Hz), 4.10-4.25 (m, 1H), 2.1-2.6(m, 4H), 2.27(s, 6H), 2.7-2.95(m, 3H), 1.43(ddd, 1H, 5.7Hz, 5.7Hz and 13Hz), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3290, 2938, 1676, 1636, 1578, 1541, 1476, 1456, 1296, 1275, 1225, 1142.

Example 14

Preparation of 5-[3'-(5",6",7",8"-tetrahydro-2"-naphtoxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 45 in Table 1):

The reaction was effected with 3-(5',6',7',8'-tetrahydro-2'-naphtoxy)benzoic acid (324 mg, 1.21 mmol) in the same manner as in Example 7 to give the titled compound (131 mg, yield 24%).

m.p.141-151°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.30-7.50(m, 3H), 7.20(br-s, 1H), 7.11(ddd, 1H, 1.5Hz, 2.5Hz, 7.8Hz), 7.04(d, 1H, 8.1Hz), 6.70-6.80 (m, 2H), 5.97(d, 1H, 9.7Hz), 5.92(br-s, 1H), 4.12-4.25(m, 1H), 2.7- 2.8(m, 4H), 2.54(dd, 1H, 4.7Hz, 18.1Hz), 2.2-2.5(m, 3H), 1.70-2.0 (m, 7H), 1.45(ddd, 1H, 5.2Hz, 5.2Hz and 12.5Hz), 1.02(s, 3H)
IR(KBr):ν(cm^{-1})=3287, 2934, 2859, 2633, 1674, 1636, 1580, 1557, 1497, 1481, 1427, 1306, 1275, 1248, 1188, 1146.

Example 15

Preparation of 5-(3'-benzyloxy-benzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 46 in Table 1):

The reaction was effected with 3-benzyloxybenzoic acid (516 mg, 2.26 mmol) in the same manner as in Example

1 to give the titled compound (325 mg, yield 34.5%).

m.p.175-177°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.30-7.47(m, 8H), 7.21(s, 1H), 7.13 (dd, 1H, 2.5Hz, 8.0Hz), 5.99(d, 1H, J=9.7Hz), 5.92(t, 1H, J=3.7Hz), 5.13(s, 2H), 4.16-4.26(m, 1H), 2.31-2.60(m, 4H), 1.80-1.92(m, 3H), 1.47(dt, 1H, J=5.5Hz, 12.8Hz)
IR(KBr):ν(cm^{-1})=3291, 3065, 3036, 2942, 2910, 2870, 1680, 1640, 1611, 1580, 1549, 1483, 1454, 1426, 1304, 1285, 1235.

Example 16

Preparation of 5-(3'-diphenylmethyloxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 50 in Table 1):
The reaction was effected with 3-diphenylmethyloxybenzoic acid (498 mg, 1.64 mmol) in the same manner as in Example 1 to give the titled compound (204 mg, yield 25%).

m.p.89-91°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.5(m, 14H), 7.0-7.1(m, 1H), 6.25(s, 1H), 5.8-5.9(m, 2H), 4.0-4.2(m, 1H), 2.1-2.6 (m, 4H), 2.7-2.9(m, 3H), 1.35-1.5(m, 1H), 0.96(s, 3H)
IR(KBr):ν(cm^{-1})=3308, 3063, 3030, 2934, 1684, 1634, 1580, 1524, 1483, 1454, 1429, 1273, 1233, 1186, 1020, 748, 700.

Example 17

Preparation of 5-(3'-cyclopentyloxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 51 in Table 1):
The reaction was effected with 3-cyclopentyloxybenzoic acid (413 mg, 2.0 mmol) in the same manner as in Example 1 to give the titled compound (230 mg, yield 29%).

m.p.175-176°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.26-7.36(m, 3H), 7.21(s, 1H), 7.02(dd, 1H, J=2.5Hz, 8.0Hz), 6.01(d, 1H, J=9.7Hz), 5.92(t, 1H, J=3.7Hz), 4.80-4.88(m, 1H), 4.16-4.26(m, 1H), 2.22-2.59(m, 3H), 1.56-2.00(m, 12H), 1.46(dt, 1H, J=5.5Hz, 12.8Hz), 1.03(s, 3H)
R(KBr):ν(cm^{-1})=3291, 2936, 2870, 1680, 1636, 1589, 1555, 1485, 1426, 1319, 1275, 1242.

Example 18

Preparation of 5-(3'-cyclohexyloxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 63 in Table 1):
The reaction was effected with 3-cyclohexyloxybenzoic acid (530 mg, 2.41 mmol) in the same manner as in Example 1 to give the titled compound (292 mg, yield 29.0%).

m.p.192-194 °C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.21-7.37(m, 4H), 7.04(dd, 1H, 2.5Hz, 8.0Hz), 6.01(d, 1H, J=9.3Hz), 5.92(t, 1H, J=3.7Hz), 4.15-4.38 (m, 2H), 2.21-2.59(m, 4H), 1.76-2.05(m, 7H), 1.29-1.64(m, 7H), 1.03(s, 3H)
IR(KBr):ν(cm^{-1})=3312, 2936, 2865, 1672, 1636, 1609, 1576, 1539, 1481, 1429, 1304, 1287, 1236, 1051.

Example 19

Preparation of 5-(3'-cycloheptyloxybenzoylamino)-10-methy-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 111 in Table 1):
The reaction was effected with 3-cycloheptyloxybenzoic acid (2.17 mg, 9.26 mmol) in the same manner as in Example 7 to give the titled compound (2.8 mg, yield 71%).

m.p.224-226 °C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.4(m, 4H), 6.98-7.02(m, 1H), 6.01(br-d, 1H, 9.7Hz), 5.92(t-like 1H, J≒1.0Hz), 4.20-4.35(m, 1H), 4.1-4.3(m, 1H), 2.1-2.6(m, 4H), 2.0-2.1(m, 2H), 1.3-1.9(m, 8H), 1.03(s, 3H)
IR(KBr):ν(cm^{-1})=3304, 2932, 2863, 1674, 1638, 1609, 1576, 1545, 1483, 1456, 1427, 1323, 1306, 1277, 1236,

1188, 1022, 750.

Example 20

Preparation of 5-(3'-cyclooctyloxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 159 in Table 1):

The reaction was effected with 3-cyclooctyloxybenzoic acid (268 mg, 1.08 mmol) in the same manner as in Example 7 to give the titled compound (358 mg, yield 76%).

m.p.214-218°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.2-7.35(m, 3H), 7.17(d, 1H, 1.4Hz), 7.00(dd, 1H, 2.4Hz, 8.0Hz), 5.98(d, 1H, 10Hz), 5.90(t, 1H, 3.6Hz), 4.4-4.5(m, 1H), 4.18(ddd, 1H, 5.2Hz, 10Hz and 10Hz), 2.53(dd, 1H, 5.6Hz, 19Hz), 2.1-2.4(m, 3H), 1.4-2.0(m, 18H), 1.01(s, 3H)
IR(KBr):ν(cm^{-1})=3299, 2928, 1676, 1638, 1609, 1576, 1549, 1478, 1424, 1323, 1287.

Example 21

Preparation of 5-[3'-(4-methylcyclohexyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 207 in Table 1):

The reaction was effected with 3-(4-methylcyclohexyloxy) benzoic acid (423 mg, 1.81 mmol) in the same manner as in Example 1 to give the titled compound (375 mg, yield 49.0%).

m.p.194-199°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.21-7.40(m, 4H), 7.06(dd, 1H, J=2.5Hz, 8.0Hz), 5.92(t, 1H, J=3.7Hz), 5.51(d, 1H, J=9.7Hz), 4.14-4.61(m, 2H), 2.23-2.60(m, 3H), 1.34-2.07(m, 14H), 1.03 (s, 3H), 0.94(d, 3H, J=5.0Hz)
IR(KBr):ν(cm^{-1})=3293, 2932, 2870, 2633, 1674, 1637, 1578, 1545, 1481, 1427, 1277, 1236, 1124, 1036.

Example 22

Preparation of 5-[3-(4-isopropylcyclohexyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 255 in Table 1):

The reaction was effected with 3-(4-isopropylcyclohexyloxy)benzoic acid (474 mg, 1.81 mmol) in the same manner as in Example 1 to give the titled compound (185 mg, yield 23%).

m.p.128-129°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.20-7.40(m, 4H), 7.10(s-like, 1H), 6.95-7.05(m, 1H), 5.99(br-d, 1H, 9.8Hz), 5.86(t-like, 1H, J≒1Hz), 4.1-4.3(m, 2H), 2.1-2.6(m, 6H), 1.8-2.0(m, 5H), 1.1-1.6(m, 7H), 1.02(s, 3H), 0.88(s, 6H)
IR(KBr):ν(cm^{-1})=3324, 2938, 2868, 2627, 1678, 1636, 1580, 1535, 1483, 1431, 1275, 1238, 1132, 1080, 1040, 1003.

Example 23

Preparation of 5-[3-(4-trans-t-butylcyclohexyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 303 in Table 1):

The reaction was effected with 3-(4-trans-t-butylcyclo-hexyloxy)benzoic acid (237 mg, 0.86 mmol) in the same manner as in Example 1 to give the titled compound (154 mg, yield 38.5%).

m.p.129-134°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.21-7.39(m, 4H), 7.04(ddd, 1H, J=2.5Hz, 2.5Hz, 8.0Hz), 6.03(d, 1H, 9.7Hz), 5.92(t, 1H, J=3.7Hz), 4.14-4.29(m, 1H), 2.15-2.61(m, 6H), 1.82-1.96(m, 5H), 1.31-1.54 (m, 3H), 1.09-1.18(m, 3H), 1.03 (s, 3H), 0.88(s, 9H)
IR(KBr):ν(cm^{-1})=3439, 2946, 2866, 1678, 1638, 1582, 1528, 1481, 1275, 1236, 1049, 1030.

Example 24

Preparation of 5-[3'-(4''-cis-t-butylcyclohexyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 351 in Table 1):

The reaction was effected with 3-(4-cis-t-butylcyclohexyloxy)benzoic acid (320 mg, 1.16 mmol) in the same manner as in Example 1 to give the titled compound (102 mg, yield 52.6%).

m.p.137-139°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.21-7.37(m, 4H), 7.06(ddd, 1H, J=2.5Hz, 2.5Hz, 8Hz), 5.92(t, 1H, J=3.7Hz), 4.61(br s, 1H), 4.16-4.27 (m, 1H), 2.06-2.62(m, 7Hz), 1.81-1.96(m, 3H), 1.39-1.62(m, 7H), 1.03(s, 3H), 0.88(s, 9H)
IR(KBr):ν(cm^{-1})=3319, 2943, 2868, 1676, 1636, 1582, 1530, 1481, 1429, 1306, 1273, 1236, 1182, 1007.

Example 25

Preparation of 5-[3'-(N-acetyl-3''-piperidinyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 299 in Table 1):

The reaction was effected with 3-(N-acetyl-3'-piperidinyloxy)benzoic acid (203 mg, 0.77 mmol) in the same manner as in Example 7 to give the titled compound (303 mg, yield 87%).

m.p.68-72°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.40(d-like, 1H), 7.35(d, 1H, 7.9Hz), 7.25-7.29(m, 1H), 7.19(d, 1H, 1.5Hz), 7.06(ddd, 1H, 1.6Hz, 0.8Hz, 7.1Hz), 6.02(br-d, 1H, 9.7Hz), 5.93(t, 1H, 3.7Hz), 4.61-4.67 (m, 1H), 4.14-4.23(m, 1H), 3.3-3.9 (m, 4H), 2.1-2.6(m, 4H), 2.13 (s, 1H), 1.7-2.0(m, 3H), 1.4-1.6(m, 1H), 1.04(s, 3H)
IR(KBr):ν(cm^{-1})=3384, 2934, 1698, 1632, 1580, 1539, 1483, 1454, 1364, 1318, 1233, 1034.

Example 26

Preparation of 5-[3'-(N-methyl-3''-piperidinyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 401 in Table 1):

The reaction was effected with 3-(N-methyl-3'-piperidinyloxy)benzoic acid (168 mg, 0.62 mmol) in the same manner as in Example 7 to give the titled compound (70 mg, yield 26%).

m.p.63-65°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.35-7.45(m, 3H), 7.11(d, 1H, 1.9Hz), 7.08(ddd, 1H, 2.7Hz, 2.5Hz, 6.5Hz), 6.84(br-d, 1H, 9.6Hz), 5.88 (br-s, 1H), 4.75(br-s, 1H), 4.1-4.3(m, 1H), 3.2-3.4(m, 4H), 2.82 (s, 3H), 1.8-2.6(m, 11H), 1.4-1.6 (m, 1H), 1.04(s, 3H)
IR(KBr):ν(cm^{-1})=3420, 2938, 2722, 1692, 1640, 1582, 1537, 1481, 1235, 1040, 754, 691.

Example 27

Preparation of 5-[3'-(3''-tetrahydropyranyl)oxybenzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 403 in Table 1):

The reaction was effected with 3-(3'-tetrahydropyranyl) oxybenzoic acid (313 mg, 1.41 mmol) in the same manner as in Example 7 to give the titled compound (229 mg, yield 39%).

m.p.83-85°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.39(d, 1H, 1.4Hz), 7.34(d, 1H, 7.8Hz), 7.20(s-like, 1H), 7.06(ddd, 1H, 1.3Hz, 1.1Hz, 8.2Hz), 6.03(d, 1H, 9.6Hz), 5.92(s-like, 1H), 4.5-4.7(m, 1H), 4.1-4.3(m, 1H), 3.9-4.1 (m, 2H), 3.5-3.7(m, 2H), 1.7-2.6 (m, 11H), 1.3-1.5(m, 1H), 1.03(s, 3H)
IR(KBr):ν(cm^{-1})=3422, 2934, 1688, 1636, 1580, 1539, 1483, 1431, 1304, 1233, 1186.

Example 28

Preparation of 5-[3'-(4''-heptyloxy)phenoxybenzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 423 in Table 1):

The reaction was effected with 3-(4'-heptyloxy)phenoxybenzoic acid (296 mg, 1.26 mmol) in the same manner as in Example 7 to give the titled compound (297 mg, yield 56%).

m.p.153-156°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.3(m, 4H), 7.00(dd, 1H, 1.4Hz, 8.0Hz), 5.98(d, 1H, 10Hz), 5.90(t, 1H, 3.4Hz), 4.31(t, IH, 5.7Hz), 4.18(ddd, 1H, 5.2Hz, 10Hz and 10Hz), 2.53(dd, 1H, 5.6Hz, 18.7Hz), 2.1-2.5(m, 3H), 1.3-2.0(m, 12H), 1.01(s, 3H), 0.90(t, 6H, 7.2Hz)

IR(KBr):ν(cm^{-1})=3297, 2959, 2872, 1684, 1636, 1580, 1541, 1305, 1277, 1235.

Example 29

Preparation of 5-[3'-(2",4"-dimethyl-3"-pentyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 481 in Table 1):

The reaction was effected with 3-(2',4'-dimethyl-3'-pentyloxy)benzoic acid (235 mg, 0.99 mmol) in the same manner as in Example 7 to give the titled compound (203 mg, yield 51%).

m.p.190-192°C
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.10-7.40(m, 4H), 7.04(dd, IH, 2.7Hz, 8.1Hz), 5.97(d, IH, 9.6Hz), 5.90(dd, 1H, each 3.7Hz), 4.10-4.15(m, 1H), 3.96(t, IH, 5.8Hz), 2.1-2.6(m, 4H), 1.3-2.1(m, 6H), 1.01, 0.96, 0.93, 0.90(each s, each 3H), 0.92(s, 6H)
IR(KBr):ν(cm^{-1})=3347, 2965, 1682, 1638, 1578, 1541, 1508, 1474, 1458, 1426, 1285, 1236, 1123.

Example 30

Preparation of 5-(3'-dicyclopropylmethoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 529 in Table 1):

The reaction was effected with 3-dicyclopropylmethoxybenzoic acid (307 mg, 1.32 mmol) in the same manner as in Example 7 to give the titled compound (203 mg, yield 36%).

m.p.129-132°C
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.23-7.40(m, 3H), 7.18(br-s, 1H), 7.03(ddd, 1H, 1.5Hz, 6.0Hz, 7.4Hz), 5.98(d, 1H, 9.65Hz), 5.90 (br-s, 1H), 4.12-4.23(m, 1H), 3.53(t, 1H, 7.0Hz), 2.52(dd, 1H, 5.2Hz, 18Hz), 2.1-2.5(m, 3H), 1.7-1.95 (m, 3H), 1.44(ddd, 1H, 5.5Hz, 5.5Hz and 13.1Hz), 1.0-1.2(m, 2H), 1.01(s, 3H), 0.6-0.8(m, 4H), 0.4-0.6(m, 4H)
IR(KBr):ν(cm^{-1})=3341, 3081, 3009, 2938, 1672, 1634, 1580, 1545, 1485, 1429, 1304, 1233, 1211, 1003, 982.

Example 31

Preparation of 5-(3'-cyclohexylmethoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 424 in Table 1):

The reaction was effected with 3-cyclohexylmethoxybenzoic acid (472 mg, 2.01 mmol) in the same manner as in Example 7 to give the titled compound (406 mg, yield 48%).

m.p.159-161°C
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.1-7.4(m, 4H), 7.01(dd, 1H, 1.3Hz, 7.0Hz), 5.99(d, 1H, 9.7Hz), 5.90(dd, 1H, each 3.9Hz), 4.1-4.3(m, 1H), 3.78(d, 2H, 6.1Hz), 2.1-2.6(m, 4H), 1.6-1.95(m, 9H), 1.45(ddd, 5.5Hz, 12.7Hz and 12.7Hz), 0.90-1.30(m, 5H), 1.01(s, 3H)
IR(KBr):ν(cm^{-1})=3275, 2930, 2853, 1680, 1636, 1611, 1582, 1543, 1449, 1429, 1319, 1277, 1240, 1038.

Example 32

Preparation of 5-(3'-dicyclohexylmethoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 442 in Table 1):

The reaction was effected with 3-dicyclohexylmethoxybenzoic acid (293 mg, 0.93 mmol) in the same manner as in Example 7 to give the titled compound (257 mg, yield 54%).

m.p.142-146°C
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.1-7.35(m, 4H), 7.03(dd, 1H, 1.8Hz, 8.0Hz), 5.98(d, 1H, 9.7Hz), 5.90(dd, 1H, each 3.6Hz), 4.1-4.3(m, 1H), 3.99(t, 1H, 5.8Hz), 2.1-2.6(m, 4H), 1.5-1.95(m, 15H), 1.4-1.5 (m, 1H), 1.0-1.3(m, 10H), 1.02(s, 3H)
IR(KBr):ν(cm^{-1})=3447, 2928, 2853, 1682, 1636, 1580, 1541, 1522, 1481, 1456, 1316, 1277, 1235.

Example 33

Preparation of 5-[3'-(1"-morpholinomethyl)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 577 in Table 1):

The reaction was effected with 3-(1-morpholinomethyl)benzoic acid (500 mg, 2.26 mmol) in the same manner as in Example 1 to give the titled compound (327 mg, yield 35.1%).

m.p. (amorphous)
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.76(s, 1H), 7.64(d, 1H, J=7.5Hz), 7.50(d, 1H, J=7.5Hz), 7.40(t, 1H, J=7.5Hz), 7.10 (d, 1H, J=1.9Hz), 5.87(t, 1H, J=3.5Hz), 3.91-4.25(m, 5H), 3.70(s, 2H, 2.85-3.17 (m, 4H), 2.16-2.54(m, 4H), 1.81-1.92(m, 3H), 1.36-1.51(m, 1H), 1.12(s, 3H)
IR(KBr):ν(cm^{-1})=3395, 2935, 1687, 1642, 1539, 1454, 1304, 1263, 1213, 1127, 1078.

Example 34

Preparation of 5-[3'-(1"-piperidinomethyl)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 578 in Table 1):

The reaction was effected with 3-(1-piperidinomethyl)benzoic acid (338 mg, 1.54 mmol) in the same manner as in Example 1 to give the titled compound (328 mg, yield 52.2%).

m.p. (amorphous)
^{1}H-NMR($CDCl_3$, 250MHz)δ=8.54(s, 1H), 7.96(t, 1H, J=1.8Hz), 7.39, 7.51(m, 3H), 7.11(d, 1H, J=1.9Hz), 5.82(t, 1H, J=3.5Hz), 4.00-4.28(m, 3H), 2.84-3.22(m, 4H), 1.76-2.53(m, 9H), 1.54-1.71 (m, 2H), 1.35-1.50(m, 1H), 1.12(s, 3H)
IR(KBr):ν(cm^{-1})=3422, 2942, 1644, 1541, 1454, 1316, 1213, 1046.

Example 35

Preparation of 5-(3'-cyclohexylmethylbenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 579 in Table 1):

The reaction was effected with 3-cyclohexylmethylbenzoic acid (352 mg, 1.61 mmol) in the same manner as in Example 7 to give the titled compound (296 mg, yield 63%).

m.p.182-183°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.45-7.60(m, 2H), 7.15-7.40(m, 3H), 5.98(d, 1H, 12.2Hz), 5.90(br-s, 1H), 4.1-4.3(m, 1H), 2.52(d, 2H, 6.9Hz), 2.1-2.6(m, 4H), 1.35-2.00(m, 10H), 0.8-1.3(m, 5H), 1.02(s, 3H)
IR(KBr):ν(cm^{-1})=3277, 2924, 2851, 1674, 1634, 1541, 1451, 1426, 1306, 1275.

Example 36

Preparation of 5-(3'-cycloheptylmethylbenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 581 in Table 1):

The reaction was effected with 3-cycloheptylmethyl benzoic acid (50.8 mg, 0.219 mmol) in the same manner as in Example 7 to give the titled compound (45.5mg, yield 49%).

m.p.171-173°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.59(br-s, 1H), 7.52(ddd, 1H, 1.2Hz, 1.2Hz and 8.0Hz), 7.1-7.4(m, 3H), 5.98(d, 1H, 8.9Hz), 5.92(br-s, 1H), 2.57(d, 2H, 7.2Hz), 2.1-2.6(m, 4H), 1.1-1.95(m, 17H), 1.02(s, 3H)
IR(KBr):ν(cm^{-1})=3293, 2922, 2853, 1684, 1636, 1541, 1458, 1275, 1088.

Example 37

Preparation of 5-[3-bromo-5-(p-isopropylphenoxy) benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 596 in Table 1):

The reaction was effected with 3-bromo-5-(p-isopropylphenoxy)benzoic acid (498 mg, 1.49 mmol) in the same manner as in Example 1 to give the titled compound (520 mg, yield 67%).

m.p.62-65°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.51(dd, 1H, each 1.4Hz), 7.31(dd, 1H, each 1.4Hz), 7.15-7.25(m, 4H), 6.95(d, 2H, 8.6Hz), 5.85-5.95(m, 2H), 4.05-4.20(m, 1H), 2.84-2.97(m, 1H), 2.1-2.6(m, 4H), 2.75-2.90 (m, 3H), 1.35-2.50(m, 1H), 1.23, 1.26(each s, each 3H)
IR(KBr):ν(cm^{-1})=3308, 3079, 2961, 1682, 1638, 1570, 1541, 1426, 1305, 1277, 1238, 1206, 1171, 858.

Example 38

Preparation of 5-[3',5'-di(p-isopropylphenoxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 597 in Table 1):

The reaction was effected with 3,5-di(p-isopropylphenoxy)benzoic acid (478 mg, 1.22 mmol) in the same manner as in Example 1 to give the titled compound (340 mg, yield 48%).

m.p.158-159°C
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.10-7.20(m, 5H), 7.02(d, 2H, 2.2Hz), 6.94(d, 4H, 8.6Hz), 6.71(dd, 1H, each 2.2Hz), 5.82-5.90(m, 2H), 4.02 -4.20(m, 1H), 2.80-2.95(m, 2H), 2.10-2.60(m, 4H), 2.70-2.90(m, 3H), 1.30-1.50(m, 3H), 1.30-1.50(m, 1H), 1.21, 1.24(each s, each 3H), 0.95(s, 3H)
IR(KBr):ν(cm^{-1})=3291, 2963, 2936, 2872, 1682, 1640, 1609, 1588, 1555, 1505, 1435, 1327, 1283, 1217, 1173, 1123, 1005, 835.

Example 39

Preparation of 5-(3'-cycloheptyloxy-4'-methoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 139 in Table 1):

The reaction was effected with 3-cycloheptyloxy-4-methoxybenzoic acid (319 mg, 1.21 mmol) in the same manner as in Example 7 to give the titled compound (278 mg, yield 50%).

m.p.127-129°C
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.38(d, 1H, 2.0Hz), 7.17-7.21(m, 2H), 6.85(d, 1H, 8.5Hz), 5.89-5.95(m, 2H), 4.39-4.50 (m, 1H), 4.11-4.23 (m, 1H), 3.87(s, 3H), 2.52(dd, 1H, 5.0Hz, 18.1Hz), 2.01-2.48(m, 5H), 1.35-1.95(m, 14H), 1.01 (s, 3H)
IR(KBr):ν(cm^{-1})=3447, 3291, 2932, 2861, 1680, 1634, 1507, 1269.

Example 40

Preparation of 5-(3',4'-methylenedioxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 491 in Table 1):

The reaction was effected with piperonylic acid (217 mg, 1.31 mmol) in the same manner as in Example 7 to give the titled compound (293 mg, yield 61%).

m.p.(amorphous)
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.20-7.30(m, 2H), 7.18(d, 1H, 1.7Hz), 6.82(d, 1H, 7.4Hz), 6.01(s, 2H), 5.91-5.95(m, 2H), 4.10-4.21(m, 1H), 4.52(dd, 1H, 4.1Hz, 18Hz), 2.1-2.5(m, 3H), 1.75-1.95(m, 3H), 1.42(ddd, 1H, 5.5Hz, 12.7Hz and 12.7Hz), 1,00(s, 3H)
IR(KBr):ν(cm^{-1})=3314, 2934, 1699, 1636, 1541, 1505, 1487, 1439, 1259, 1209, 1182, 1038.

Example 41

Preparation of 5-(3',4'-ethylenedioxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 493 in Table 1):

The reaction was effected with 3,4-ethylenedioxybenzoic acid (214 mg, 1.19 mmol) in the same manner as in Example 7 to give the titled compound (188 mg, yield 43%).

m.p.(amorphous)
^{1}H-NMR(CDCl$_3$, 250MHz)δ=7.27-7.30(m, 2H), 7.17(br-s, 1H), 6.89(d, 1H, 8.3Hz), 5.84-5.90(m, 2H), 4.27(s, 4H), 4.08-4.25 (m, 1H), 2.51(dd, 1H, 4.5Hz, 18.4Hz), 2.10-2.47(m, 3H), 1.75-1.90 (m, 3H), 1.42(ddd, 1H, 5.7Hz, 5.7Hz, 13.1Hz), 1.00(s, 3H)
IR(KBr):ν(cm^{-1})=3341, 2936, 1684, 1634, 1615, 1582, 1541, 1501, 1316, 1289, 1260, 1067.

Example 42

Preparation of 5-(3',4'-cyclohexylidenedioxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 495 in Table 1):

The reaction was effected with 3,4-cyclohexylidenedioxybenzoic acid (303 mg, 1.29 mmol) in the same manner

as in Example 7 to give the titled compound (250 mg, yield 46%).

m.p.104-105°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.24(dd, 1H, 1.8Hz, 8.1Hz), 7.14-7.18 (m, 2H), 6.73(d, 1H, 8.1Hz), 5.8-5.95(m, 2H), 4.15(ddd, 1H, 4.9Hz, 10Hz and 10Hz), 2.51(dd, 1H, 5.3Hz, 19Hz), 2.15-2.45(m, 3H), 1.82-1.95 (m, 7H), 1.35-1.60 (m, 5H), 0.99(s, 3H)
IR(KBr):ν(cm^{-1})=3301, 2940, 1866, 1674, 1636, 1559, 1541, 1491, 1437, 1360, 1306, 1283, 1258.

Example 43

Preparation of 5-(3',5'-di-t-butylbenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 503 in Table 1):

The reaction was effected with 3,5-di-t-butylbenzoic acid (243 mg, 1.04 mmol) in the same manner as in Example 7 to give the titled compound (143 mg, yield 32%).

m.p.99-101°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.55-7.57(m, 3H), 7.18(br-s, 1H), 5.90-5.96(m, 2H), 4.16-4.30(m, 1H), 2.53(dd, 1H, 5.0Hz, 19Hz), 2.10-2.50(m, 3H), 1.70-1.90(m, 3H), 1.46(ddd, 1H, 5.7Hz, 5.7Hz, 13Hz), 1.34(s, 18H), 1.02(s, 3H)
IR(KBr):ν(cm^{-1})=3293, 2961, 1682, 1634, 1595, 1539, 1474, 1458, 1424, 1364, 1265, 1213, 706.

Example 44

Preparation of 5-(5',6',7',8'-tetrahydro-5',5',8',8'-tetramethylnaphthalene-2'-carbonylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 509 in Table 1):

The reaction was effected with 5,6,7,8-tetrahydro-5,5, 8,8-tetramethylnaphthalene-2-carboxylic acid (207 mg, 0.89 mmol) in the same manner as in Example 7 to give the titled compound (232 mg, yield 62%).

m.p.109-110°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.80(d, 1H, 1.8Hz), 7.41(dd, 1H, 1.9Hz, 8.2Hz), 7.33(d, 1H, 8.2Hz), 7.17(d, 1H, 1.5Hz), 5.95(d, 1H, 9.7Hz), 5.90(dd, 1H, each 3.7Hz), 4.10-4.25(m, 1H), 2.10-2.60(m, 4H), 1.78 -1.95(m, 3H), 1.68(s, 4H), 1.44(ddd, 1H, 5.5Hz, 12.7Hz and 12.7Hz), 1.29, 1.30(each s, each 3H), 1.27(s, 6H), 1.01(s, 3H)
IR(KBr):ν(cm^{-1})=3310, 2961, 1684, 1634, 1559, 1539, 1267.

Example 45

Preparation of (5R,10R)-5-(3'-cycloheptyloxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 111 in Table 1):

The reaction was effected with 3-cycloheptyloxybenzoic acid (359 mg, 1.53 mmol) and (5R,10R)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (339 mg, 1.53 mmol) in the same manner as in Example 7 to give the titled compound (370 mg, yield 57%).

$[\alpha]_D^{26}$=+135°(c=0.50, MeOH)
m.p.133-135°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.4(m, 4H), 6.98-7.02(m, 1H), 6.01(br-d, 1H, 9.7Hz), 5.92(t-like, 1H, J≒1.0Hz), 4.20-4.35(m, 1H), 4.1-4.3(m, 1H), 2.1-2.6(m, 4H), 2.0-2.1(m, 2H), 1.3-1.9(m, 8H), 1.03(s, 3H).

Example 46

Preparation of (5S,10S)-5-(3'-cycloheptyloxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 111 in Table 1):

The reaction was effected with 3-cycloheptyloxybenzoic acid (280 mg, 1.19 mmol) and (5S,10S)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (264 mg, 1.19 mmol) in the same manner as in Example 7 to give the titled compound (271 mg, yield 54%).

$[\alpha]_D^{26}$=-128°(c=0.50, MeOH)
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.4(m, 4H, 6.98-7.02(m, 1H), 6.01(br-d, 1H, 9.7Hz), 5.92(t-like, 1H, J≒1.0Hz), 4.20-4.35 (m, 1H), 4.1-4.3(m, 1H), 2.1-2.6(m, 4H), 2.0-2.1(m, 2H), 1.3-1.9 (m, 8H), 1.03(s, 3H).

Example 47

Preparation of (5S,10S)-5-(3'-dicyclopropylmethoxybenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 529 in Table 1):

The reaction was effected with 3-dicyclopropylmethoxybenzoic acid (105 mg, 0.48 mmol) and (5S,10S)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (110 mg, 0.48 mmol) in the same manner as in Example 7 to give the titled compound (56 mg, yield 27%).

$[\alpha]_D^{27}$ =-126°(c=0.50, MeOH)
m.p.97-99°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.23-7.40(m, 3H), 7.18(br-s, 1H), 7.03(ddd, 1H, 1.5Hz, 6.0Hz, 7.4Hz), 5.98(d, 1H, 9.65Hz), 5.90(br-s, 1H), 4.12-4.23(m, 1H), 3.53(t, 1H, 7.0Hz), 2.52(dd, 1H, 5.2Hz, 18Hz), 2.1-2.5(m, 3H), 1.7-1.95 (m, 3H), 1.44(ddd, IH, 5.5Hz, 5.5Hz and 13.1Hz), 1.0-1.2(m, 2H), 1.01(s, 3H), 0.6-0.8(m, 4H), 0.4-0.6(m, 4H).

Example 48

Preparation of (5S,10S)-5-[3'-(2",4"-dimethyl-3"-pentyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 481 in Table 1):

The reaction was effected with 3-(2',4'-dimethy-3'-pentyloxy)benzoic acid (124 mg, 0.52 mmol) and (5S,10S)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (116 mg, 0.52 mmol) in the same manner as in Example 7 to give the titled compound (216 mg, yield 66%).

$[\alpha]_D^{27}$ =-170°(c=1.0, MeOH)
m.p.116-118°C
^{1}H-NMR($CDCR_3$, 250MHz)δ=7.10-7.40(m, 4H), 7.04(dd, 1H, 2.7Hz, 8.1Hz), 5.97(d, 1H, 9.6Hz), 5.90(dd, 1H, each 3.7Hz), 4.10-4.15(m, 1H), 3.96(t, 1H, 5.8Hz), 2.1-2.6(m, 4H), 1.3-2.1(m, 6H), 1.01, 0.96, 0.93, 0.90(each s, each 3H), 0.92(s, 6H)
IR(KBr):ν(cm^{-1})=3328, 2965, 2874, 1682, 1634, 1580, 1532, 1481, 1429, 1316, 1275, 1236, 1213, 1186, 1005, 752.

Example 49

Preparation of (5S,10S)-N-methyl-5-[3'-(2",4"-dimethyl-3"-pentyloxy)benzoylamino]-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 497 in Table 1):

The reaction was effected with 3-(2',4'-dimethy-3'-pentyloxy)benzoic acid (137 mg, 0.58 mmol) and (5S,10S)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (128 mg, 0.58 mmol) in the same manner as in Example 7 to give the titled compound (238 mg, yield 99%). This compound was dissolved in dimethylformamide (1 ml) and mixed with sodium hydride (27 mg, 0.66 mmol), 0.5 hours later mixed with methyl iodide (0.055 ml, 0.89 mmol), and the resultant mixture was stirred for 3 hours. The reaction mixture was poured into chilled water, extracted with diethyl ether, and the extract was concentrated. The product was hydrolyzed and purified in the same manner as in Example 7 to give the titled compound (170 mg, yield 70%).

$[\alpha]_D^{27}$=-166°(c=0.33, MeOH)
m.p.(amorphous)
^{1}H-NMR($CDCl_3$, DMSO-d_6, 373K, 250MHz)δ=7.27(dd, 1H, each 7.9Hz), 6.96(dd, 1H, 1.8Hz, 7.9Hz), 6.80-6.90(m, 3H), 5.76(br-s, 1H), 5.76(br-s, 1H), 3.99(t, 1H, 5.6Hz), 2.90(s, 3H), 2.1-2.5(m, 5H), 1.9-2.1(m, 2H), 1.65-1.85(m, 2H), 1.1-1.3(m, 1H), 1.05(s, 3H), 0.9-1.0(m, 12H)
IR(KBr):ν(cm^{-1})=2965, 2874, 1701, 1684, 1634, 1578, 1456, 1404, 1364, 1316, 1256, 1209, 1005, 980, 793, 754.

Example 50

Preparation of 5-(3'-cycloheptyloxy-4'-isopropyloxy-benzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 117 in Table 1):

The reaction was effected with 3-cycloheptyloxy-4-isopropyloxybenzoic acid (157 mg, 0.54 mmol) and 5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (125 mg, 0.54 mmol) in the same manner as in Example 7 to give the titled compound (128 mg, yield 48%).

m.p.143-196°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.38(d, 1H, 2.1Hz), 7.23(dd, 1H, 2.1Hz, 8.3Hz), 7.19(br-s, 1H), 6.89(d, 1H, 8.3Hz),

5.90-5.95 (m, 2H), 4.49-4.62(m, 1H), 4.30-4.46(m, 1H), 4.12-4.23(m, 1H), 2.53(dd, 1H, 5.1Hz, 19Hz), 2.15-2.48 (m, 3H), 1.3-2.1(m, 16H), 1.32, 1.34(each s, each 3H), 1.01(s, 3H)
IR(KBr):ν(cm^{-1})=2976, 2932, 2859, 1682, 1634, 1601, 1499, 1302, 1217, 1138, 1107, 1001, 954.

Example 51

Preparation of 5-(3'-cycloheptyloxy-2-methylbenzoylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 119 in Table 1):

The reaction was effected with 3-cycloheptyloxy-2-methylbenzoic acid (200 mg, 0.81 mmol) in the same manner as in Example 1 to give the titled compound (297 mg, yield 84.1%).

m.p.237-239°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.20(s, 1H), 7.16(dd, 1H, J=7.2Hz, 8.3Hz), 6.91(d, 1H, J=7.2Hz), 6.86(d, 1H, J=8.3Hz), 5.92(t, 1H, J=3.7Hz), 5.64(d, 1H, J=9.7Hz), 4.40-4.49(m, 1H), 4.14-4.24(m, 1H), 2.16-2.66(m, 3H), 2.29 (s, 3H), 1.40-2.07(m, 17H), 0.96(s, 3H)
IR(KBr):ν(cm^{-1})=3277, 2932, 2858, 1672, 1634, 1541, 1458, 1425, 1308, 1260, 1186, 1078.

Example 52

Preparation of (1S,8S)-1-(3'-cycloheptyloxybenzoylamino)-8a-methyl-1,2,6,7-tetrahydroindene-5-carboxylic acid (Compound No. 135 in Table 1):

The reaction was effected with 3-cycloheptyloxybenzoic acid (104 mg, 0.44 mmol) and (1S,8S)-1-amino-8a-methyl-1,2,6,7-tetrahydroindene-5-carboxylic acid methyl ester (92 mg, 0.44 mmol) in the same manner as in Example 7 to give the titled compound (18 mg, yield 9.3%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.3(m, 4H), 6.89(dd, 1H, 1.8Hz, 7.4Hz), 6.73(br-d, IH, 8.7Hz), 6.04(br-s, 1H), 4.3-4.5(m, 2H), 2.63(ddd, 1H, 3Hz, 7.6Hz, 17Hz), 2.1-2.5(m, 3H), 1.85-2.0(m, 3H), 1.30-1.8(m, 2H), 0.92(s, 1H)
IR(KBr):ν(cm^{-1})=3380, 2930, 2857, 1686, 1640, 1580, 1483, 1238, 1181, 1086, 1019, 696.

Example 53

Preparation of (1S,8S)-1-[3'-(2",4"-dimethyl-3"-pentyl)oxybenzoylamino]-8a-methyl-1,2,6,7-tetrahydroindene-5-carboxylic acid (Compound No. 505 in Table 1):

The reaction was effected with 3-(2',4'-dimethyl-3'-pentyl)oxybenzoic acid (64 mg, 0.27 mmol) and 1-amino-8a-methyl-1,2,6,7-tetrahydroindene-5-carboxylic acid methyl ester (56 mg, 0.27 mmol) in the same manner as in Example 7 to give the titled compound (25 mg, yield 22%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.1-7.4(m, 4H), 7.05(dd, 1H, 1.8Hz, 8.1Hz), 6.21(d, 1H, 8.8Hz), 5.87(br-s, 1H), 4.45-4.6(m, IH), 3.96 (t, IH, 5.7Hz), 2.81(ddd, 1H, 3.0Hz, 7.6Hz, 16.8Hz), 2.3-2.7(m, 3H), 1.9-2.1(m, 3H), 1.59(ddd, 5.7Hz, 5.7Hz and 12.5Hz), 0.96, 0.95, 0.93, 0.92, 0.90(each s, each 3H)
IR(KBr):ν(cm^{-1})=3374, 2965, 1686, 1638, 1580, 1539, 1481, 1283, 1240, 1198, 1003, 754.

Example 54

Preparation of (1S,8S)-1-[3'-(dicyclopropylmethyloxy)benzoylamino]-8a-methyl-1,2,6,7-tetrahydroindene-5-carboxylic acid (Compound No. 553 in Table 1):

The reaction was effected with 3-(dicyclopropylmethyloxy)benzoic acid (72 mg, 0.31 mmol) and 1-amino-8a-methyl-1,2,6,7-tetrahydroindene-5-carboxylic acid methyl ester (64 mg, 0.31 mmol) in the same manner as in Example 7 to give the titled compound (29 mg, yield 22%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.2-7.4(m, 4H), 7.05(ddd, 1H, 2.2Hz, 2.2Hz, and 6.9Hz), 6.21(d, 1H, 8.9Hz), 5.87(br-s, 1H), 4.47-4.59 (m, 1H), 3.53(t, 1H, 7.0Hz), 2.81(ddd, 1H, 3Hz, 7.8Hz, 17Hz), 2.2-2.7(m, 3H), 2.04(dd, 1H, 4.2Hz, 13Hz), 1.59(ddd, 5.7Hz, 5.7Hz, and 12.5Hz), 1.0-1:2(m, 2H), 1.03(s, 3H), 0.4-0.6(m, 4H), 0.2-0.4(m, 4H)
IR(KBr):ν(cm^{-1})=3364, 3083, 3009, 2961, 2930, 1686, 1638, 1582, 1539, 1483, 1296, 1240, 1198.

Example 55

Preparation of 5-(3'-cycloheptyloxybenzenesulfonylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Com-

pound No. 620 in Table 1):

To a mixture of 5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (108 mg, 0.49 mmol), triethylamine (0.65 ml) and methylene chloride (2.6 ml) was added 3-cycloheptyloxybenzenesulfonyl chloride (129 mg, 0.47 mmol), and the resultant mixture was stirred at room temperature for 1 hour, poured into chilled water and extracted with ethyl acetate. The extract was concentrated, and the residue was chromatographed on a silica gel column to give crude product (88 mg). This product was hydrolyzed in the same manner as in Example 7 to give the titled compound (62 mg, yield 30%).

m.p.124-125°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.30-7.40(m, 3H), 7.09(br-s, 1H), 7.03(ddd, 1H, 2.4Hz and 6.8Hz), 5.77(t, 1H, 3.7Hz), 4.4-4.5(m, 1H), 4.38(br-d, 1H, 9.8Hz), 3.05-3.20(m, 1H), 2.45(dd, 1H, 5.1Hz, 18.4Hz), 2.1-2.3(m, 3H), 1.3-2.1(m, 15H), 0.95-1.10(m, 1H), 0.87(s, 3H)
IR(KBr):ν(cm^{-1})=3268, 2932, 2863, 2631, 2540, 1682, 1632, 1613, 1476, 1431, 1323, 1289, 1252, 1236, 1157, 1096, 1063.

Example 56

Preparation of (5S,10S)-5-(3'-cycloheptyloxybenzene-sulfonylamino)-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid (Compound No. 620 in Table 1):

The reaction was effected with 3-cycloheptyloxy benzenesulfonyl chloride (142 mg, 0.51 mmol) and (5S,10S)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester (87 mg, 0.40 mmol) in the same manner as in Example 55 to give the titled compound (82 mg, yield 46%).

m.p.70-72°C
^{1}H-NMR($CDCl_3$, 250MHz)δ=7.30-7.40(m, 3H), 7.09(br-s, 1H), 7.03(ddd, 1H, 2.4Hz and 6.8Hz), 5.77(t, 1H, 3.7Hz), 4.4-4.5(m, 1H), 4.38(br-d, 1H, 9.8Hz), 3.05-3.20(m, 1H), 2.45(dd, 1H, 5.1Hz, 18.4Hz), 2.1-2.3(m, 3H), 1.3-2.1(m, 15H), 0.95-1.10(m, 1H), 0.87(s, 3H).

Example 57

Preparation of 5-(3'-phenoxybenzoylamino)-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (Compound No. 624 in Table 2):

The reaction was effected with 3-phenoxybenzoic acid (0.91 mg, 4.23 mmol) and 1-amino-6-trifluoromethanesulfonyl-1,2,3,4-tetrahydronaphthalene (1.5 g, 5.08 mmol) to give the condensation product (1.5 g, 73%). This product (0.537 mg, 1.09 mmol) was added to a mixture of palladium acetate (123 mg, 0.55 mmol), triphenyl phosphine (286 mg, 1.1 mmol), triethylamine (19.4 ml), methanol (50 ml) and tetrahydrofuran (50 ml), and the resultant mixture was reacted in an atmosphere of carbon monoxide for 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was concentrated, and the residue was hydrolyzed in the same manner as in Example 7 to give the titled compound (88 mg, yield 21%).

m.p.155-160°C
^{1}H-NMR($CDCl_3$+catCD_3OD, 250MHz)δ=7.81(d-like, 2H, 4Hz), 7.30-7.55(m, 5H), 7.10-7.20(m, 2H), 6.95-7.10(m, 2H), 6.62-6.78 (m, 1H), 5.30-5.45(m, 1H), 2.80-2.95(m, 2H), 2.1-2.3(m, 1H), 2.85-2.95(m, 3H)
IR(KBr):ν(cm^{-1})=3274, 2936, 1694, 1632, 1578, 1534, 1481, 1429, 1269, 1233, 1200, 752, 691.

Example 58

Preparation of 5-(3'-phenoxybenzoyl)amino-9-methyl-$\Delta^{1(2),8(9)}$-octalin-2-(2'-trans-propenoic acid) (Compound No. 640 in Table 3):

To a mixture of 3-phenoxybenzoic acid (93 mg, 0.44 mmol), triethylamine (0.31 ml, 2.2 mmol) and methylene chloride (3 ml) chilled at 0°C was gradually added thionyl chloride (48 μl, 0.66 mmol), and the resultant mixture was stirred at 0°C for 15 minutes. A solution of 5-amino-9-methyl-$\Delta^{1(2),8(9)}$-octalin-2-(2'-propenoic acid) methyl ester (114 mg, 0.44 mmol) in methylene chloride (3 ml) was added to the mixture, which was stirred at room temperature for 30 minutes. The reaction mixture was distributed between ethyl acetate and water, and the organic layer was washed with saturated brine and concentrated. The residue was dissolved in methanol (5 ml), mixed with 2 N aqueous KOH (1 ml) and refluxed under heating for 1 hour. The reaction mixture was acidified with 2 N hydrochloric acid, extracted with chloroform, dried and concentrated. The resulting residue was chromatographed on a silica gel column, eluting with chloroform-methanol to give the titled compound (60 mg, yield 32%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.34-7.49(m, 6H), 7.15(t, 2H, J=7.5Hz), 7.03(d, 2H, J=7.5Hz), 6.36(br s, 1H), 5.98(d, 1H, J=9.7Hz), 5.85(d, 1H, J=15.7Hz), 5.77(t, 1H, J=3.7Hz), 4.16-4.31(m, 1H), 2.15-2.59(m, 3H), 1.82-1.92(m, 4H), 1.41-1.54(m, 1H), 1.03(s, 3H)

IR(KBr):ν(cm^{-1})=3426, 3289, 3065, 2938, 1674, 1634, 1605, 1580, 1547, 1481, 1318, 1277, 1232.

Example 59

Preparation of 1-[5'-(3''-phenoxybenzoylamino)-5',6', 7',8'-tetrahydro-2'-naphthyloxy]acetic acid (Compound No. 656 in Table 4):

The reaction was effected with 3-phenoxybenzoic acid (436 mg, 2.04 mmol) and 1-(5-amino-5',6',7',8'-tetrahydro-2'-naphthyloxy)acetic acid methyl ester (479 mg, 2.04 mmol) in the same manner as in Example 1 to give the titled compound (300 mg, yield 35%).

m.p.153-1 57°C

^{1}H-NMR($CDCl_3$+catDMSO-d_6, 250MHz)δ=7.35-7.45(m, 1H), 6.80-7.25(m, 9H), 6.58(dd, 1H, 2.7Hz, 8.5Hz), 5.1-5.2(m, 1H), 4.41(s, 2H), 2.5-2.7(m, 2H), 1.5-2.0(m, 4H)

IR(KBr):ν(cm^{-1})=3343, 2932, 2866, 1725, 1611, 1574, 1549, 1481, 1435, 1333, 1289, 1186, 1163, 1132, 1080, 760, 694.

Example 60

Preparation of 1-[5'-(3''-benzyloxybenzoylamino)-5',6',7',8'-tetrahydro-2'-naphthyloxy]acetic acid (Compound No. 666 in Table 4):

The reaction was effected with 3-benzyloxybenzoic acid (398 mg, 1.74 mmol) and 1-(5'-amino-5',6',7',8'-tetrahydro-2'-naphthyloxy)acetic acid methyl ester (410 mg, 1.74 mmol) in the same manner as in Example 1 to give the titled compound (127 mg, yield 17%).

m.p.(amorphous)

^{1}H-NMR($CDCl_3$+catDMSO-d_6, 250MHz)δ=7.1-7.4(m, 8H), 6.95-7.05 (m, 1H), 6.5-6.8(m, 3H), 5.15-5.25(m, 1H), 5.01(s, 2H), 4.47(s, 2H), 2.6-2.8(m, 2H), 1.95-2.10(m, 1H), 1.7-1.9(m, 3H)

IR(KBr):ν(cm^{-1})=3345, 2928, 2859, 1723, 1613, 1578, 1551, 1499, 1445, 1290, 1240, 1217, 1163, 1132, 1080, 1017, 756, 698.

Reference Example 1

Preparation of 5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester:

To a mixture of Wieland Mischer's ketone (38.5 g, 216 mmol), diisopropylethylamine (39.5 ml) and methylene chloride (770 ml) was added anhydrous trifluoromethanesulfonic acid (40 ml, 238 mmol) under ice cooling, and the resultant mixture was stirred at room temperature for 2 hours. The reaction mixture was mixed with hexane (120 ml), and the organic layer was washed with water, 3 N hydrochloric acid, saturated aqueous sodium bicarbonate solution and saturated brine in this order, dried and concentrated to give monoenol triflate compound (63 g). This product was dissolved in a mixture of methanol (630 ml) and tetrahydrofuran (630 ml), mixed with palladium acetate (1.14 g, 5.08 mmol), trifphenyl phosphine (2.6 g, 10.1 mmol) and triethylamine (315 ml). Carbon monoxide was bubbled into the solution at room temperature for 50 hours. Then, the reaction mixture was diluted with hexane, poured into chilled water and extracted with ethyl acetate to give light yellow syrup (33 g). This product was dissolved in methanol (1.3 L), mixed with ammonium acetate (115 g, 1.45 mmol) and sodium cyanoborohydride (6.4 g, 102 mmol), and the mixture was refluxed for 6 hours. The reaction mixture was allowed to warm at room temperature, poured into chilled water and extracted with chloroform under weakly basic conditions. The organic layer was dried and concentrated. The residue was washed with hexane-diethyl ether to give the titled compound (16.2 g, yield 34%) as white powders.

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.05(d, 1H), 5.78(t, 1H), 3.73(s, 3H), 2.62(d, 1H), 2.57(dd, 1H), 2.2-2.4(m, 3H), 1.95 (ddd-like, 1H), 1.5-1.8(m, 3H), 1.1-1.3(m, 2H), 0.86(s, 3H).

Reference Example 2

Preparation of (5S,10S)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester:

The reaction was effected with (+)-Wieland Mischer's ketone (Fulka Company, $[\alpha]_D$ > +98° (c = 1.0, benzene) (2.0 g, 11.2 mmol) in the same manner as in Reference Example 1 to give the titled compound (0.95 g, yield 57%).

$[\alpha]_D{}^{27}$ =-254°(c=0.50, MeOH)

Reference Example 3

Preparation of (5R,10R)-5-amino-10-methyl-$\Delta^{1(2),8(9)}$-octalin-2-carboxylic acid methyl ester:

The racemate obtained in Reference Example 1 (2.27 g, 10.3 mmol) was recrystallized three times together with L-benzoyltartaric acid (3.86 g, 10.3 ml) in methanol. The crystals are collected under basic conditions and purified to give the titled compound (339 mg, yield 15%).

$[\alpha]_D^{26}$ =+244°(c=0.5, MeOH)

Reference Example 4

Preparation of (1S,8S)-l-amino-8a-methyl-1,2,6,7-tetrahydro-indane-5-carboxylic acid methyl ester:

The reaction was effected with (+)-2,3,6,7-tetrahydro-8a-methyl-1,5-indadione ($[\alpha]_D^{29}$ > +358° (c = 1.0, benzene) (2.95 g, 18.0 mmol) in the same manner as in Reference Example 1 to give the titled compound (408 g, yield 11%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.19(d, 1H, 2.4Hz), 5.74(br-s-like), 3.72(s, 3H), 3.10(dd, 1H, 7.6Hz, 10.0Hz), 1.8-2.7 (m, 4H), 1.2-1.4 (m, 2H), 0.81(s, 3H).

Reference Example 5

Preparation of 1-(1'-amino-1',2',3',4'-tetrahydro-2'-naphthyloxy)acetic acid methyl ester:

The reductive animation was effected with 1-(1'-oxo-1',2',3',4'-tetrahydro-2'-naphthyloxy)acetic acid methyl ester (9.0 g, 36.2 mmol), prepared from α-bromoacetic acid and 6-hydroxytetralone, in the same manner as in Reference Example 1 to give the titled compound (4.08 g, yield 48%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.13(1H, d, 8.6Hz), 6.67(1H, dd, 2.7Hz and 8.6Hz), 6.56(d, 1H, 2.7Hz), 4.97-5.10 (m, 1H), 4.55(s, 2H), 3.75 (s, 3H), 2.60-2.80(m, 2H), 1.65-2.05(m, 4H).

Reference Example 6

Preparation of 5-amino-9-methyl-$\Delta^{1(2),8(9)}$-octalin-2-(2'-propenylic acid) ethyl ester:

To a solution of palladium acetate (126 mg, 0.56 mmol), triphenyl phosphine (292 mg, 1.12 mmol) and tetrahydrofuran (2.9 ml) previously prepared was dropwise added a solution of enol triflate (1.74 g, 5.61 mmol) as disclosed in Reference Example 1 in tetrahydrofuran (10 ml). The mixture was mixed with triethylamine (10 ml) and ethyl acetate (1.22 ml, 11.2 mmol), and stirred at room temperature for 3 days. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with water and saturated sodium bicarbonate solution, dried and concentrated. The residue was chromatographed on a silica gel column (40 g) eluting with hexane-ethyl acetate to give 5-oxo-9-methyl-$\Delta^{1(2),8(9)}$-octalin-2-(2'-propenoic acid) ethyl ester (0.6 g, yield 35%). This product was subjected to reductive amination in the manner as disclosed in Reference Example 1 to give the titled compound (114 mg, yield 22%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.33(d, 1H, 15.7Hz), 6.31(s, 1H), 6.86(d, 1H, 15.7Hz), 5.70(t, 1H, 3.8Hz), 4.21(q, 2H, 7.1Hz), 2.83 (dd, 1H, 5.6Hz, 10.4Hz), 2.2-2.4(m, 5H), 2.0-2.18(m, 1H), 1.7-1.9 (m, 2H), 1.30(t, 3H, 7.1Hz), 0.99 (s, 3H).

Reference Example 7

Preparation of 3-(p-t-butylphenoxy)benzoic acid:

To a solution of 3-bromobenzonitrile (4.35 g, 23.9 mmol) and p-t-butylphenol (4.30 g, 28.7 mmol) in pyridine (45 ml) were added potassium carbonate (6.61 g, 47.8 mmol) and cupric oxide (3.42 g, 43 mmol), and the resultant mixture was refluxed for 46 hours. The reaction mixture was poured into saturated potassium hydrogensulfate solution and extracted with ethyl acetate. The organic layer was concentrated, and the residue was dissolved in ethylene glycol (20 ml), mixed with 2 N potassium hydroxide solution (130 ml) and refluxed for 20 hours. The reaction mixture was poured into chilled water and extracted with diethyl ether under acidic conditions. The organic layer was dried and concentrated. The residue was chromatographed on a silica gel column to give the titled compound (3.46 g, yield 54%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.80(d-like, 1H, 7.6Hz), 7.70(t, 1H, 1.9Hz), 7.42(d, 1H, 7.6Hz), 7.36(d, 2H, 8.6Hz), 7.24(dd, 1H, 1.9Hz, 7.6Hz), 6.94(d, 2H, 8.6Hz), 1.32(s, 9H).

The compounds of the following Reference Examples 8 - 16 were prepared according to Reference Example 7.

Reference Example 8

4-phenoxybenzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.98(d, 2H, 8.8Hz), 7.34(t, 2H, 7.7Hz), 7.14(t, 1H, 7.7Hz), 7.02(d, 2H, 8.8Hz), 6.93

(d, 2H, 7.7Hz), 3.83 (br-s, 1H).

Reference Example 9

3-(o-isopropylphenoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.77(d, 1H, 7.8Hz), 7.61(br-s, 1H), 7.40(d, 1H, 8.0Hz), 7.35(t-like, 1H, 4.9Hz), 7.1-7.2 (m, 3H), 6.85-6.90(m, 1H), 3.15-3.3(m, 1H), 1.19, 1.22(each s, each 3H).

Reference Example 10

3-(p-isopropylphenoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.80(ddd, 1H, 1.2Hz, 1.6Hz, 7.8Hz), 7.68(dd, 1H, 1.6Hz, 2.4Hz), 7.39(dd, 1H, 7.8Hz, 8.0Hz), 7.18-7.28 (m, 3H), 6.90-7.0(m, 2H), 2.80-3.00(m, 1H), 1.23, 1.26(each s, each 3H).

Reference Example 11

3-(m-isopropylphenoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.83(ddd, 1H, 1.2Hz, 1.5Hz, 7.7Hz), 7.72(dd, 1H, 1.2Hz, 2.8Hz), 7.42(dd, 1H, 7.9Hz, 8.0Hz), 7.2-7.3(m, 2H), 7.02(dd, -like, 1H, 0.7Hz, 7.2Hz), 6.92(br-s, 1H), 6.82(dd- like, 1.2Hz, 8.2Hz), 2.80-3.00(m, 1H), 1.23, 1.26(each s, each 3H).

Reference Example 12

3-[p-(2'-methylpropyl)phenoxy]benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.89(ddd, 1H, 1.2Hz, 1.7Hz, 7.7Hz), 7.67(dd, 1H, 2.4Hz, 1.7Hz), 7.40(t, 1H, 7.7Hz), 7.21(ddd, 1H, 1.2Hz, 2.4Hz, 7.7Hz), 7.11(d, 2H, 8.5Hz), 6.92(d, 2H, 8.5Hz), 3.75(br-s, 1H), 2.45(d, 2H, 7.2Hz), 1.84 (dt, 1H, 6.5Hz, 7.2Hz), 0.90(d, 6H, 6.5Hz).

Reference Example 13

3-(p-tolyloxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.79(ddd, 1H, 1.2Hz, 1.6Hz, 7.7Hz), 7.65(dd, 1H, 1.6Hz, 2.4Hz), 7.39(t, 1H, 7.7Hz), 7.21(ddd, 1.2Hz, 1.8Hz, 7.7Hz), 7.15(d, 2H, 8.6Hz), 6.92(d, 2H, 8.6Hz), 2.34(s, 3H).

Reference Example 14

3-(p-cyclohexylphenoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.80(dd-like, 1H, 1.2Hz, 8.0Hz), 7.68(dd, 1H, 1.2Hz, 2.4Hz), 7.39(t, 1H, 8.0Hz), 7.10-7.25(m, 3H), 6.93(d, 2H, 8.6Hz), 2.38-2.58(m, 1H), 1.68-1.96(m, 5H), 1.14-1.52 (m, 5H).

Reference Example 15

3-(2',4'-dimethylphenoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.81(dd, 1H, 1.6Hz, 7.7Hz), 7.68 (dd, 1H, 1.6Hz, 2.2Hz), 7.40(dd, 1H, 7.7Hz, 7.9Hz), 7.22(dd-like, 2.2Hz, 7.9Hz), 6.77(br-s, 1H), 6.63(br-s, 2H), 2.28(s, 6H).

Reference Example 16

3-(5',6',7',8'-tetrahydro-2'-naphthyloxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.79(br-d, 1H, 7.7Hz), 7.67(br-s, 1H), 7.40(t, 1H, 7.7Hz), 7.23(dd, 1H, 2.4Hz, 7.7Hz), 7.04(d, 1H, 8.0Hz), 6.7-6.8(m, 2H), 2.7-2.8(m, 4H), 1.7-1.9(m, 4H).

Reference Example 17

Preparation of 3-bromo-5-(p-isopropylphenoxy)benzoic acid (a) and 3,5-di(p-isopropylphenoxy)benzoic acid (b):

To a solution of 3,5-dibromobenzoic acid (3.8 g, 11 mmol) and p-isopropylphenol (3.36 g, 24.2 mmol) in pyridine (46 ml) were added cupric oxide (2.19 g, 27.5 mmol) and potassium carbonate (6.08 g, 44 mmol), and the resultant mixture was refluxed for 5 days. The reaction mixture was allowed to warm up to room temperature, poured into chilled

water and extracted with chloroform under acidic conditions. The organic layer was concentrated, and the residue was chromatographed on a silica gel column to give the titled compounds (a) (489 mg, yield 13%) and (b) (1.88 g, yield 44%).

(a); ^{1}H-NMR($CDCl_3$, 250MHz)δ=7.19(dd, 1H, each 1.7Hz), 7.60 (dd, 1H, each 1.7Hz), 7.34(dd, 1H, each 1.7Hz), 7.23(d, 2H, 8.2Hz), 6.95(d, 2H, 8.2Hz), 2.8-3.0(m, 1H), 1.24, 1.27(each s, each 3H)
(b); ^{1}H-NMR($CDCl_3$, 250MHz)δ=7.34(d, 2H, 2.1Hz), 7.19(m, 4H, 8.5Hz), 6.94(d, 4H, 8.5Hz), 6.86(d, 1H, 2.1Hz), 2.80-2.95(m, 2H), 1.22, 1.25(each s, each 6H).

Reference Example 18

Preparation of 3-dicyclohexylmethoxybenzoic acid:

To a solution of 3-hydroxybenzoic acid (1.61 g, 8.2 mmol), dicyclohexylmethanol (1.61 g, 8.2 mmol), triphenylphosphine (2.05 g, 7.82 mmol) and dioxane (35 ml) was added diethyl azodicarboxylate (1.41 ml, 8.94 mmol), and the resultant mixture was refluxed for 3 days. The reaction mixture was allowed to warm up to room temperature, poured into chilled water and extracted with diethyl ether. The organic layer was concentrated, and the residue was dissolved in a mixture of methanol (20 ml), tetrahydrofuran (6.5 ml) and water (2.0 ml), mixed with potassium hydroxide (1.16 g) and stirred for 2 hours. The mixture was poured into chilled water, acidified, and extracted with ethyl acetate. The organic layer was concentrated, and the resultant residue was recrystallized from hexane to give the titled compound (0.43 g, yield 18 %).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.55-7.65(m, 2H), 7.30(dd, 1H, each 8.4Hz), 7.13(ddd, 1H, 0.9Hz, 2.5Hz, 8.4Hz), 3.98(t, 1H, 5.6Hz), 1.50-1.88(m, 12H), 0.96-1.34(m, 10H).

The compounds of the following Reference Examples 19 - 24 were prepared according to Reference Example 18.

Reference Example 19

3-(2',4'-dimethyl-3'-pentoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.55-7.65(m, 2H), 7.32(t, 1H, 8.2Hz), 7.15(ddd, 1H, 1.0Hz, 2.7Hz, 8.2Hz), 3.94(t, 1H, 5.8Hz), 2.01(dt, 2H, 6.8Hz, 13.3Hz), 0.90-0.98(m, 12H).

Reference Example 20

3-(dicyclopropylmethoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.50-7.61(m, 2H), 7.28(t, 1H, 8.2Hz), 7.10(ddd, 1H, 1.2Hz, 2.7Hz, 8.2Hz), 3.88(s, 3H), 3.49(t, 1H, 6.9Hz), 1.0-1.2(m, 2H), 0.4-0.6(m, 4H), 0.2-0.4(m, 4H).

Reference Example 21

3-(cyclooctyloxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.66(ddd, 1H, 1.2Hz, 2.3Hz and 8.0Hz), 7.57(dd, 1H, 2.3Hz, 1.7Hz), 7.34(t, 8Hz), 7.09(ddd, 1.2Hz, 1.7Hz, 8.0Hz), 4.47(4.0Hz, 7.9Hz, 11.8Hz), 1.4-2.0(m, 14H).

Reference Example 22

3-(4-heptyloxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.64(ddd, 1.2Hz, 2.0Hz, 8.0Hz), 7.59(dd, 1H, 1.2Hz, 2.3Hz), 7.33(t, 1H, 8.0Hz), 7.10 (ddd, 1.2Hz, 2.3Hz, 8.9Hz), 4.31(dt, 1H, 5.9Hz, 11.6Hz), 1.3-1.8(m, 8H), 0.91 (t, 6H, 7.0Hz).

Reference Example 23

3-(cyclohexylmethoxy)benzoic acid:

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.68(1H, 2.2Hz, 7.7Hz), 7.60(d, 1H, 2.2Hz), 7.35(t, 1H, 7.7Hz), 7.12(dt, 1H, 2.0Hz, 7.7Hz), 3.79(d, 2H, 6.0Hz), 1.6-1.9(m, 6H), 1.0-1.4(m, 5H).

Reference Example 24

3-cycloheptyloxy-4-methoxybenzoic acid:

^{1}H-NNR($CDCl_3$, 250MHz)δ=7.63(dd, 1H, 2.0Hz, 8.5Hz), 7.50(d, 1H, 2.0Hz), 6.86(d, 1H, 8.5Hz), 4.42(ddd, 1H, 4.3Hz, 8.5Hz and 12.6Hz), 3.88(s, 3H), 3.86(s, 3H), 1.96-2.05(m, 2H), 1.62-1.94(m, 4H), 1.33 -1.62(m, 6H).

Reference Example 25

Preparation of 3-isopropyl-4-cycloheptylbenzoic acid:

To a solution of 3,4-dihydroxybenzoic acid ethyl ester (2.0 g, 11 mmol) in acetone (450 l) were added potassium carbonate (2.28 g, 16.5 mmol) and isopropylamide (1.03 ml, 11 mmol), and the resultant mixture was stirred at room temperature for 2 days. The reaction mixture was poured into chilled water and extracted with ethyl acetate under acidic conditions. The organic layer was concentrated, and the residue was chromatographed on a silica gel column to give a mixture (617 mg) of 3-hydroxy-4-isopropyloxybenzoic acid ethyl ester and its position isomer, 4-hydroxy-3-isopropyloxybenzoic acid ethyl ester (6:1). There was observed NOE of protons at 1'-position of the isopropyl group and 5-position. The reaction was effected using this mixture (617 mg) in the same manner as in Reference Example 18, and the resultant product was recrystallized from hexane to give the titled compound (370 mg, yield 12%).

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.68(dd, 1H, 2.0Hz, 8.4Hz), 7.58(d, 1H, 2.0Hz), 6.90(d, 1H, 8.4Hz), 4.55-4.70(m, 1H), 4.35-4.50(m, 1H), 1.9-2.1(m, 2H), 1.3-1.9(m, 10H), 1.34-1.37(each s, each 3H).

Reference Example 26

Preparation of 3-cyclohexylmethylbenzoic acid:

To a solution of 3-carboxybenzaldehyde (2.65 g, 17.7 mmol) in tetrahydrofuran (2.65 ml) was added a solution of cyclohexyl magnesium bromide in diethyl ether (53 mmol, 30 ml). This mixture was added to 3 N hydrochloric acid (500 ml) and extracted with chloroform. The organic layer was concentrated, and the residue was chromatographed on a silica gel column to give the condensed product (1.35 g). The product was dissolved in methanol (27 ml), mixed with palladium hydroxide (135 mg) and hydrogenated. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was recrystallized from hexane to give the titled compound (0.84 g, yield 22 %).

^{1}H-NMR(-$CDCl_3$, 250MHz)δ=7.85-8.00(m, 2H), 7.30-7.40(m, 2H), 2.54(d, 2H, 6.9Hz), 1.5-1.8(m, 6H), 1.1-1.3(m, 3H), 0.80-1.05(m, 2H).

Reference Example 27

Preparation of 3-cycloheptylmethylbenzoic acid:

The titled compound was prepared according to Reference Example 26.

^{1}H-NMR($CDCl_3$, 250MHz)δ=7.85-7.95(m, 2H), 7.30-7.40(m, 2H), 2.56(d, 2H, 7.2Hz), 1.1-1.9(m, 13H).

EXPERIMENT

Human steroid 5α-reductase inhibiting effect was examined on the compounds of the present invention using human prostatic tissue.

Freozen human prostate was thawed on ice and minced into small pieces (~ 5mm^3). The minced tissue was homogenized with a Polytron homogenizer (Kinematica, Switzerland) in 40 vol. of 0.1 M phosphate buffer at pH 5.5. The suspension was used as the source of 5α-reductase.

The reaction tube contained 50nM (1α,2α-^{3}H(N))tetstosterone (2.04 TBq/mmol, New England Nuclear, MA), a predetermined amount of an inhibitor, 0.5 mg of NADPH and 0.5 ml of prostatic suspension in a total final volume of 1 ml. For this test, DMSO solutions containing various amount of the inhibitor were employed.

Each reaction solution was incubated at 37°C for 10 minutes and ethyl acetate (2 ml) chilled with ice was added for stopping the reaction. The organic layer was transferred to another test tube and evaporated to dryness under nitrogen. Each 50 µg of non radioactive testosterone, DHT, estradiol, androstenedione and androstandiol was added to the residue, and the wall of each test tube was washed with ethyl acetate (0.1 ml). The content of the tube was evaporated again and the residue was dissolved in chloroform (50 µl) and then applied to Whatman LK60DF silica plates (Whatman, NJ), developing in chloroform:methanol (50:1). The bands of the substrates and products were identified by fluorescence (254 nm) and iodine, and the relevant silica gel was collected by scraping, mixed with toluene based liquid sincilator, and the radioactivity was counted. The radioactivities of DHT and androstandiol were combined for the calculation of 5α-reductase activity. The conversion rate from testosterone to DHT and androstandiol was 35%-45% in the control group which only the solvent was added in place of inhibitors. The radioactivity for the control group was postulated as 100%.

IC_{50} were calculated from the data obtained from the above experiments. Table 5 shows the test results.

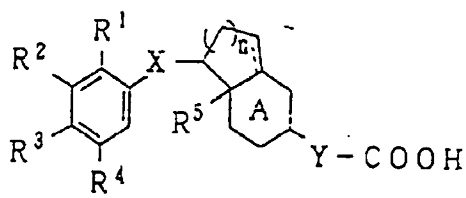
Table-5

Experiment No.	IC_{50} (μM)	Experiment No.	IC_{50} (μl)
1	3.3	23	0.30
2	0.83	31	0.41
4	0.81	35	0.16
5	0.46	37	0.30
7	0.21	39	0.39
9	0.52	42	0.77
11	0.25	43	0.23
13	0.66	45	0.61
14	0.44	46	0.30
15	4.21	47	0.16
17	0.18	48	0.065
20	0.27	51	0.91
22	0.52	54	0.16

Table 5 shows that the compounds of the present invention and salts thereof are useful as 5α-reductase inhibitors. Accordingly, they would be useful as therapeutic agents to diseases such as benign prostatic hyperplasia, acne, seborrhea, female hirsutism, prostatic cancer, male alopecia or the like, in which the reduction of DHT activity is expected to be effective for therapeutic treatment thereof.

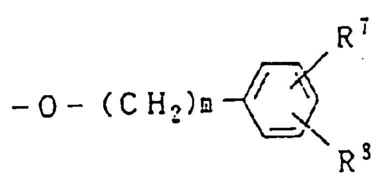
Claims

1. Carboxylic acid derivatives of the following general formula (I):

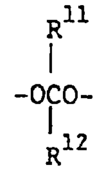


(I)

Wherein R^1, R^2, R^3 and R^4 each independently represent hydrogen atom, halogen atom, adamantyl group, optionally substituted C_1 - C_{14} alkyl group, optionally substituted C_3 - C_{10} cycloalkyl group, optionally substituted C_1 - C_{14} alkoxy group, optionally substituted heterocyclic group, - OR^6 (R^6 represents hydrogen atom, adamantyl group, optionally substituted C_3 - C_{10} cycloalkyl group or optionally substituted heterocyclic group), or a group of the formula:



wherein R^7 and R^8 each independently represent hydrogen atom, C_1 - C_6 alkyl group, C_3 - C_8 cycloalkyl group, - $CONR^9R^{10}$ (R^9 and R^{10} each independently represent hydrogen atom or C_1 - C_6 alkyl group) or, when R^7 and R^8 are adjacent, they may form C_1 - C_6-alkylene group, and m represents 0 or 1, or, the adjacent two substituents selected from R^1, R^2, R^3 and R^4 may form a group of the formula:

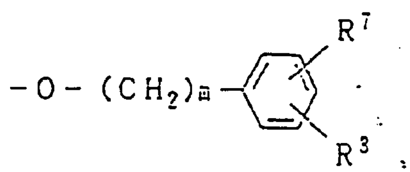


wherein R^{11} and R^{12} each independently represent hydrogen atom, C_1 - C_6 alkyl group or C_3 - C_8 cycloalkyl group, or they may form, taken together, C_2 - C_8 alkylene group, a group of the formula: $-OCH_2CH_2O-$ or optionally substituted C_3 - C_4 alkylene group,

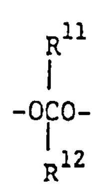
R^5 represents hydrogen atom or C_1 - C_5 alkyl group,
X represents $-CONR^{13}-$ or $-SO_2NR^{13}-$ (R^{13} represents hydrogen atom or C_1 - C_6 alkyl group),
Y represents a single bond, $-OCH_2-$ or $-CH=CH-$,
A ring may form a benzene ring, cyclohexene ring or cyclohexadiene ring,

the dotted line represents a single bond or double bond, and
n represents 1 or 2, with the proviso that when the carbon atom to which R^5 is attached has a double bond, then R^5 is not present, or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1, in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom; halogen atom; adamantyl group; C_1 - C_{14} alkyl group optionally having one or more substituents selected from 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, C_3 - C_{10} cycloalkyl group and adamantyl group; C_3 - C_{10} cycloalkyl group optionally having one or more C_1 - C_6 alkyl groups; C_1 - C_{14} alkoxy group optionally having two or more phenyl groups or one or more substituents selected from 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, C_3 -C_{10} cycloalkyl group and adamantyl group; 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom and optionally having one or more C_1 - C_6 alkyl groups; $-OR^6$ [R^5 represents hydrogen atom; adamantyl group; C_3 -C_{10} cycloalkyl group optionally having one or more C_1 - C_6 alkyl groups; or 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and optionally having one or more substituents selected from C_1 - C_6 alkyl group and C_2 - C_6 acyl group]; or a group of the formula:



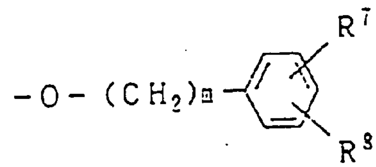
wherein R^7 and R^8 each independently represent hydrogen atom, C_3 - C_8 cycloalkyl group, $CONR^9R^{10}$ (R^9 and R^{10} each independently represent hydrogen atom or C_1 - C_6 alkyl group), or, when R^7 and R^8 are adjacent, they may form C_1 - C_6 alkylene group, and m represents 0 or 1, or, the adjacent two substituents selected from R^1, R^2, R^3 and R^4 may form a group of the formula:



wherein R^{11} and R^{12} each independently represent hydrogen atom, C_1 - C_6 alkyl group or C_3 - C_8 cycloalkyl group, or they may form, taken together, C_2 - C_8 alkylene group, a group of the formula: $-OCH_2CH_2O-$; or C_3 - C_4 alkylene

group optionally having one or more substituents selected from C_1 - C_6 alkyl group and C_3 - C_8 cycloalkyl group.

3. A compound according to Claim 2, in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom; halogen atom; C_1 - C_{14} alkyl group optionally having one or more substituents selected from 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and C_3 - C_{10} cycloalkyl group; C_1 - C_{14} alkoxy group optionally having two or more phenyl groups or one or more C_3 - C_{10} cycloalkyl groups; $-OR^6$ [R^6 represents C_3 - C_{10} cycloalkyl group optionally having one or more C_1 - C_6 alkyl groups; or 5 or 6 membered heterocyclic group containing 1 or 2 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom, and optionally having one or more C_1 - C_6 alkyl group, or a group of the formula:



wherein R^7 and R^8 each independently represent hydrogen atom, C_3 - C_8 cycloalkyl group, $-CONR^9N^{10}$ (R^9 and R^{10} each independently represents hydrogen atom or C_1 - C_6 alkyl group), or, when R^7 and R^8 are adjacent, they may form C_1 - C_6 alkylene group, and m represents 0 or 1, R^5 represents C_1 - C_6 alkyl group, X represents $-CONR^{13}-$ or $-SO_2NR^{13}-$ (R^{13} represents hydrogen or C_1 - C_6 alkyl group), and A ring may form a benzene ring or cyclohexene ring.

4. compound according to Claim 3, in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom; halogen atom; C_1 - C_{14} alkyl group optionally having one or more C_3 - C_{10} cycloalkyl group; C_1 - C_{14} alkoxy group optionally having one or more C_3 - C_{10} alkyl groups; or $-OR^6$ (R^6 represents C_1 - C_6 cycloalkyl group optionally having one or more C_1 - C_6 alkyl groups), X represents $-CONR^{13}-$ (R^{13} represents hydrogen atom), Y represents a single bond, A ring represents a cyclohexene ring, and the dotted line represents a double bond.

5. A compound according to Claim 4, in which R^1, R^2, R^3 and R^4 each independently represent hydrogen atom or C_1 - C_{14} alkoxy group and n represents 2.

6. A pharmaceutical composition comprising a carboxylic acid derivative according to Claim 1 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier therefor.

7. A therapeutic drug for treating androgen dependent diseases comprising a carboxylic acid derivative according to Claim 1 or a pharmaceutically acceptable salt thereof as an effective ingredient together with a pharmaceutically acceptable carrier therefor.

8. A therapeutic drug according to Claim 7, in which the androgen dependent disease is benign prostatic hyperplasia.

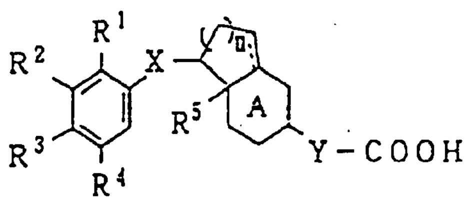
9. A therapeutic drug according to Claim 7, in which the androgen dependent disease is acne.

10. A therapeutic drug according to Claim 7, in which the androgen dependent disease is seborrhea.

11. A therapeutic drug according to Claim 7, in which the androgen dependent disease is female hirsutism.

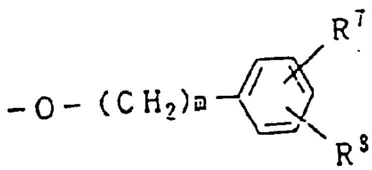
12. A therapeutic drug according to Claim 7, in which the androgen dependent disease is male alopecia.

13. A process for preparing carboxylic acid derivatives of the general formula (I):

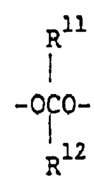


(I)

Wherein R^1, R^2, R^3 and R^4 each independently represent hydrogen atom, halogen atom, adamantyl group, optionally substituted C_1 - C_{14} alkyl group, optionally substituted C_3 - C_{10} cycloalkyl group, optionally substituted C_1 - C_{14} alkoxy group, optionally substituted heterocyclic group, - OR^6 (R^6 represents hydrogen atom, adamantyl group, optionally substituted C_3 - C_{10} cycloalkyl group or optionally substituted heterocyclic group), or a group of the formula:



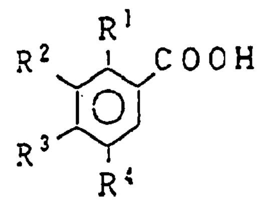
wherein R^7 and R^8 each independently represent hydrogen atom, C_1 - C_6 alkyl group, C_3 - C_8 cycloalkyl group, -$CONR^9R^{10}$ (R^9 and R^{10} each independently represent hydroge atom or C_1 - C_6 alkyl group) or, when R^7 and R^8 are adjacent, they may form C_1 - C_6 alkylene group, and m represents 0 or 1, or, the adjacent two substituents selected from R^1, R^2, R^3 and R^4 may form a group of the formula:



wherein R^{11} and R^{12} each independently represent hydrogen atom, C_1 - C_6 alkyl group or C_3 - C_8 cycloalkyl group, or they may form, taken together, C_2 - C_8 alkylene group, a group of the formula: -OCH_2CH_2O- or optionally substituted C_3 - C_4 alkylene group,

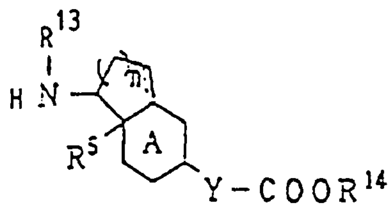
R^5 represents hydrogen atom or C_1 - C_5 alkyl group,
X represents -$CONR^{13}$- or -SO_2NR^{13}- (R^{13} represents hydrogen atom or C_1 - C_6 alkyl group),
Y represents a single bond, -OCH_2- or -CH=CH-,
A ring may form a benzene ring, cyclohexene ring or cyclohexadiene ring,

the dotted line represents a single bond or double bond, and
n represents 1 or 2, with the proviso that when the carbon atom to which R^5 is attached has a double bond, then R^5 is not present, which comprises the following steps:
condensing benzoic acid derivatives of the general formula (III):



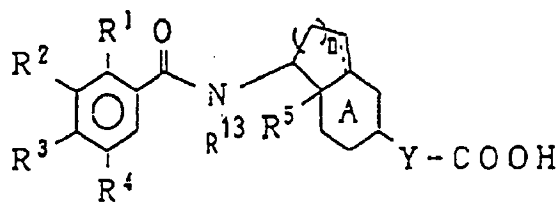
(III)

wherein R^1, R^2, R^3 and R^4 are as defined above , with amino acid derivatives of the general formula (IV):



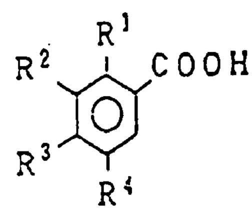
(IV)

wherein R^5 and R^{13} are as defined above, and R^{14} represents an alkyl group having 1 to 5 carbon atoms; hydrolyzing the resulting condensed product with an alkali to give the objective compound (Ia):



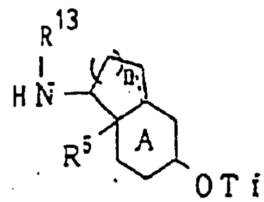
(I a)

14. A process for preparing carboxylic acid derivatives of the general formula (I) as defined in claim 13, wherein R^1, R^2, R^3, R^4, R^5, n and A have the same significance as defined in claim 13, X is represented by -CONR^{13}, wherein R^{13} is defined as in claim 13, and Y is represented by a single bond, which comprises the following steps: condensing benzoic acid derivatives of the general formula (III):



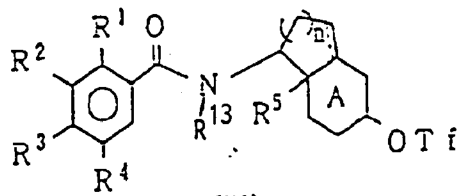
(III)

wherein R^1, R^2, R^3 and R^4 are as defined in claim 13, with amine derivatives of the general formula (V):



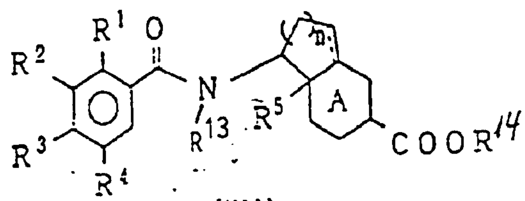
(V)

wherein R^5 and R^{13} are as defined in claim 13, and Tf represents a trifluoro-methane sulfonyl group, to give the compound of the general formula (VI):



(VI)

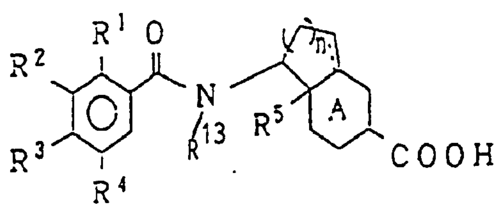
reacting the compound of the above formula (VI) with carbon monoxide in the presence of an organic base, Trialkyl phosphine and palladium (II) in an alkanol (ROH) solvent or a mixture of alkanol ($R^{14}OH$) with tetrahydrofuran, ether, or methylene chloride, wherein R^{14} represents an alkyl group of 1-5 carbon atoms, to give the ester of the general formula (VII):



(VII)

and

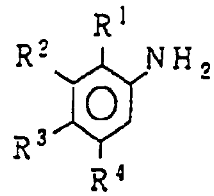
hydrolyzing the ester of the general formula (VII) with an alkali to give the objective compound of the formula (VIII):



(VIII)

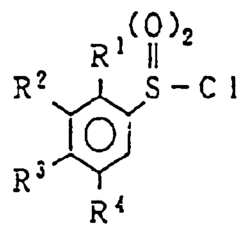
15. A process for preparing carboxylic acid derivatives of the general formula (I) as given in claim 13, wherein R^1, R^2, R^3, R^5, n, Y and A have the same significance as defined in claim 13, and X is $-SO_2NR^{13}$, wherein R^{13} is as defined in claim 13, which comprises the following steps:

reacting aniline derivatives of the general formula (IX):



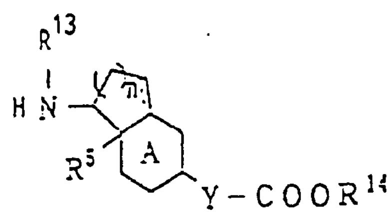
(IX)

wherein R^1, R^2, R^3 and R^4 are as defined in claim 13, with sodium nitrite or potassium nitrite to give a diazonium salt, which is reacted with cupric chloride and sulfur dioxide to give the sulfonyl chloride derivative of the general formula (X):



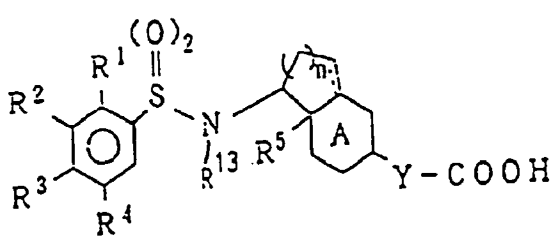
(X)

reacting the compound of the general formula (X) with a compound of the general formula (IV):



(IV)

wherein R^5 and R^{13} are as defined in claime 13, and R^{14} represents an alkyl group having 1 to 5 carbon atoms, in a halogen-type solvent and subjecting the resultant product to alkali-hydrolysis in order to result in the objective compound of the general (XI):



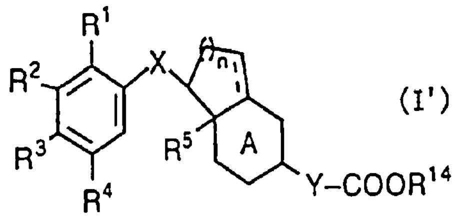
(XI)

16. The use of carboxylic acid derivatives of the general formula (I) as given in claim 13, wherein R^1, R^2, R^3, R^4, R^5,

n, Y and A are as defined in claim 13, and X is -CONR^{13}, wherein R^{13} is defined as given in claim 13, or pharmaceutically acceptable salts thereof for the preparation of a medicament effective in the treatment of androgen dependent diseases.

17. The use according to claim 16, wherein the androgen dependent disease is represented by benign prostatic hyperplasia, acne, seborrhea, female hirsutism or male alopecia.

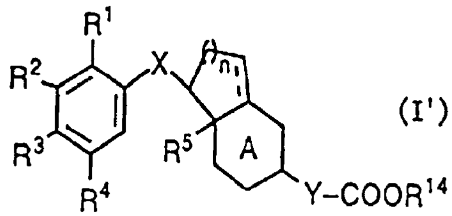
18. A compound of the formula:



(I')

wherein R^{14} is C_1-C_5 alkyl, and R^1, R^2, R^3, R^4, R^5, A, X, Y and n are as defined in claim 13.

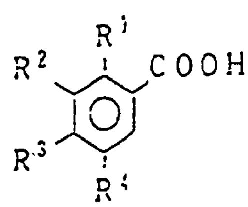
19. A process for preparing carboxylic acid derivatives of the general formula (I')



(I')

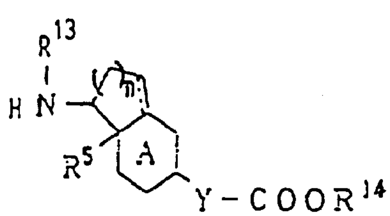
wherein R^{14} is C_1-C_5 alkyl, and R^1, R^2, R^3, R^4, R^5, A, X, Y and n are as defined in claim 13, which comprises the following steps:

condensing benzoic acid derivatives of the general formula (III):



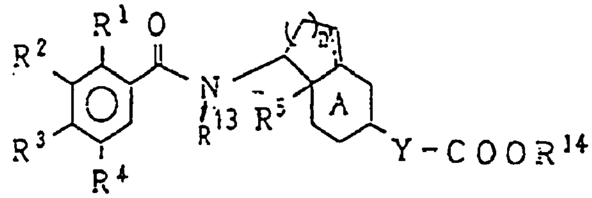
(III)

with amino acid derivatives of the general formula (IV):



(IV)

to give the objective compound (I'a):

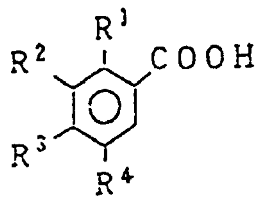


(I'a)

wherein R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A, X, Y and n are as defined above.

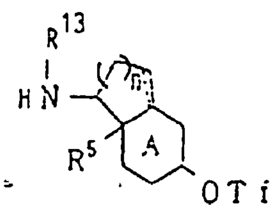
20. A process for preparing carboxylic acid derivatives of the general formula(VII) which comprises the following steps:

condensing benzoic acid derivatives of the general formula (III):



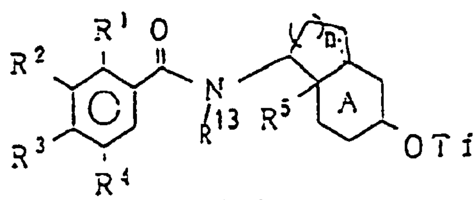
(III)

with amine derivatives of the general formula (V):



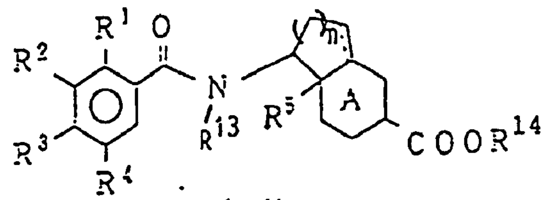
(V)

to give the compound of the general formula (VI):



(VI)

reacting the compound of the above formula (VI) with carbon monoxide in the presence of an organic base, trialkylphos phine and palladium (II) in an alkanol (ROH) solvent or a mixture of alkanol($R^{14}OH$) with tetrahydrofurane, ether, or methylene chloride, wherein R^{14} represents an alkyl group of 1-5 carbon atoms, to give the ester of the general formula (VII):

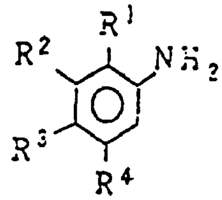


(VIi)

wherein Tf represents a trifluoro methane sulfonyl group, and R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A, and n are as defined in claim 19.

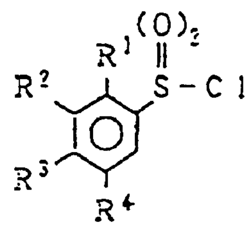
21. A process for preparing carboxylic acid derivatives of the general formula (XI') which comprises the following steps:

reacting aniline derivatives of the general formula (IX):



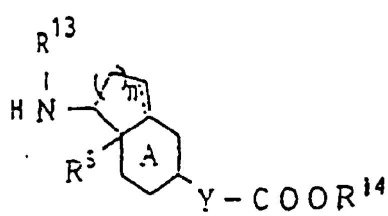
(IX)

with sodium nitrite or potassium nitrite to give a diazonium salt, which is reacted with cupric chloride and sulfur dioxide to give the sulfonyl chloride derivative of the general formula (X):



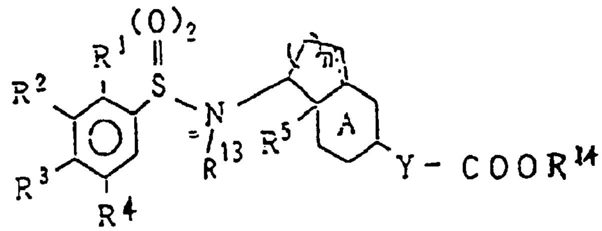
(X)

reacting the compound of the general formula (X) with a compound of the general formula (IV):



(IV)

in a halogen-type solvent to result in the objective compound of the general (XI'):

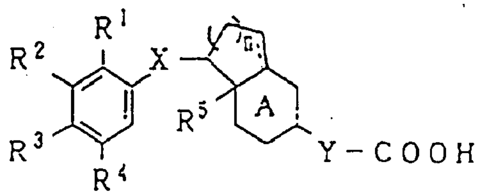


(XI')

wherein R^1,R^2,R^3,R^4,R^5,R^{13},R^{14},A,Y and n are as defined in claim 19.

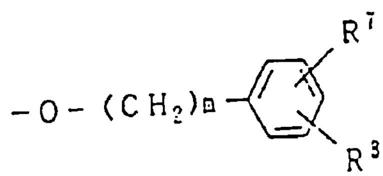
Patentansprüche

1. Carbonsäure-Derivate mit der folgenden allgemeinen Formel (I):



(I)

worin R^1, R^2, R^3 und R^4 jeweils unabhängig Wasserstoffatome, Halogenatome, Adamantyl-Gruppen, gegebenenfalls substituierte C_1-C_{14}-Alkyl-Gruppen, gegebenenfalls substituierte C_3-C_{10}-Cycloalkyl-Gruppen, gegebenenfalls substituierte C_1-C_{14}-Alkoxy-Gruppen, gegebenenfalls substituierte heterocyclische Gruppen, -OR^6 (R^6 stellt ein Wasserstoffatom, eine Adamantyl-Gruppe, eine gegebenenfalls substituierte C_3-C_{10}-Cycloalkyl-Gruppe oder eine gegebenenfalls substituierte heterocyclische Gruppe dar), oder eine Gruppe mit der Formel:



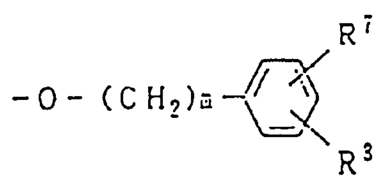
bedeuten, worin R^7 und R^8 jeweils unabhängig Wasserstoffatome, C_1-C_6-Alkyl-Gruppen, C_3-C_8-Cycloalkyl-Gruppen, -$CONR^9R^{10}$ (R^9 und R^{10} bedeuten jeweils unabhängig Wasserstoffatome oder C_1-C_6-Alkyl-Gruppen) darstellen oder, wenn R^7 und R^8 benachbart sind, sie eine C_1-C_6-Alkylen-Gruppe bilden können, und m 0 oder 1 darstellt, oder wobei zwei benachbarte Substituenten aus R^1, R^2, R^3 und R^4 eine Gruppe mit der Formel:

$$\begin{array}{c} R^{11} \\ | \\ -OCO- \\ | \\ R^{12} \end{array}$$

bilden können, worin R^{11} und R^{12} jeweils unabhängig Wasserstoffatome, C_1-C_6-Alkyl-Gruppen oder C_3-C_8-Cycloalkyl-Gruppen darstellen oder zusammengenommen eine C_2-C_8-Alkylen-Gruppe, eine Gruppe mit der Formel -OCH_2CH_2O- oder eine gegebenenfalls substituierte C_3-C_4-Alkylen-Gruppe bilden können,

R^5 ein Wasserstoffatom oder eine C_1-C_5-Alkyl-Gruppe darstellt,
X -$CONR^{13}$- oder -SO_2NR^{13}- darstellt (R^{13} bedeutet ein Wasserstoffatom oder eine C_1-C_6-Alkyl-Gruppe),
Y eine Einfachbindung, -OCH_2- oder -CH=CH- bedeutet;
der Ring A einen Benzol-Ring, Cyclohexen-Ring oder Cyclohexadien-Ring bilden kann,
die gepunktete Linie eine Einfachbindung oder eine Doppelbindung darstellt und
n 1 oder 2 darstellt, mit der Maßgabe, daß wenn das Kohlenstoffatom, an das R^5 gebunden ist, eine Doppelbindung aufweist, dann R^5 nicht vorliegt,
oder pharmazeutisch akzeptable Salze davon.

2. Verbindung gemäß Anspruch 1, worin R^1, R^2, R^3 und R^4 jeweils unabhängig bedeuten: Wasserstoffatome; Halogenatome; Adamantyl-Gruppen; C_1-C_{14}-Alkyl-Gruppen mit gegebenenfalls einem oder mehreren Substituenten, ausgewählt aus 5- oder 6gliedrigen heterocyclischen Gruppen mit 1 oder 2 Heteroatomen, ausgewählt aus Sauerstoffatomen, Schwefelatomen und Stickstoffatomen, C_3-C_{10}-Cycloalkyl-Gruppen und Adamantyl-Gruppen; C_3-C_{10}-Cycloalkyl-Gruppen mit gegebenenfalls einer oder mehreren C_1-C_6-Alkyl-Gruppen; C_1-C_{14}-Alkoxy-Gruppen mit gegebenenfalls zwei oder mehreren Phenyl-Gruppen oder einem oder mehreren Substituenten, ausgewählt aus 5- oder 6gliedrigen heterocyclischen Gruppen mit 1 oder 2 Heteroatomen, ausgewählt aus Sauerstoffatomen, Schwefelatomen und Stickstoffatomen, C_3-C_{10}-Cycloalkyl-Gruppen und Adamantyl-Gruppen; 5- oder 6gliedrige heterocyclische Gruppen mit 1 oder 2 Heteroatomen, ausgewählt aus Sauerstoffatomen, Schwefelatomen und Stickstoffatomen und gegebenenfalls mit einer oder mehreren C_1-C_6-Alkyl-Gruppen; -OR^6 [R^6 stellt ein Wasserstoffatom; eine Adamantyl-Gruppe; eine C_3-C_{10}-Cycloalkyl-Gruppe mit gegebenenfalls einer oder mehreren C_1-C_6-Alkyl-Gruppen; oder eine 5- oder 6gliedrige heterocyclische Gruppe mit 1 oder 2 Heteroatomen, ausgewählt aus Sauerstoffatomen, Schwefelatomen und Stickstoffatomen und mit gegebenenfalls einem oder mehreren Substituenten, ausgewählt aus C_1-C_6-Alkyl-Gruppen und C_{2-6}-Acyl-Gruppen, dar]; oder Gruppen mit der Formel:



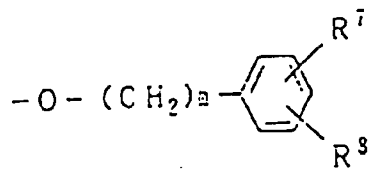
worin R^7 und R^8 jeweils unabhängig Wasserstoffatome, C_3-C_8-Cycloalkyl-Gruppen, -$CONR^9R^{10}$ (R^9 und R^{10} bedeuten jeweils unabhängig Wasserstoffatome oder C_1-C_6-Alkyl-Gruppen) darstellen, oder wenn R^7 und R^8 benachbart sind, sie eine C_1-C_6-Alkylen-Gruppe bilden können, und m 0 oder 1 darstellt, oder worin benachbarte zwei Substituenten aus R^1, R^2, R^3 und R^4 eine Gruppe mit der Formel

$$\begin{array}{c} R^{11} \\ | \\ -OCO- \\ | \\ R^{12} \end{array}$$

bilden können, worin R^{11} und R^{12} jeweils unabhängig Wasserstoffatome, C_1-C_6-Alkyl-Gruppen oder C_3-C_8-Cycloalkyl-Gruppen darstellen oder zusammengenommen eine C_2-C_8-Alkylen-Gruppe, eine Gruppe mit der Formel: -OCH_2CH_2O- oder eine C_3-C_4-Alkylen-Gruppe mit gegebenenfalls einem oder mehreren Substituenten, ausgewählt aus C_1-C_6-Alkyl-Gruppen und C_3-C_8-Cycloalkyl-Gruppen bilden können.

3. Verbindung gemäß Anspruch 2, worin R^1, R^2, R^3 und R^4 jeweils unabhängig Wasserstoffatome; Halogenatome; C_1-C_{14}-Alkyl-Gruppen mit gegebenenfalls einem oder mehreren Substituenten, ausgewählt aus 5- oder 6gliedrigen heterocyclischen Gruppen mit 1 oder 2 Heteroatomen, ausgewählt aus Sauerstoffatomen, Schwefelatomen und Stickstoffatomen, und C_3-C_{10}-Cycloalkyl-Gruppen; C_1-C_{14}-Alkoxy-Gruppen mit gegebenenfalls zwei oder mehreren Phenyl-Gruppen oder einer oder mehreren C_3-C_{10}-Cycloalkyl-Gruppen; -OR^6 [R^6 stellt eine C_3-C_{10}-Cycloalkyl-

Gruppe mit gegebenenfalls einer oder mehreren C_1-C_6-Alkyl-Gruppen; oder eine 5-oder 6gliedrige heterocyclische Gruppe mit 1 oder 2 Heteroatomen, ausgewählt aus Sauerstoffatomen, Schwefelatomen und Stickstoffatomen und mit gegebenenfalls einer oder mehreren C_1-C_6-Alkyl-Gruppen] oder eine Gruppe mit der Formel



dar, worin R^7 und R^8 jeweils unabhängig Wasserstoffatome, C_3-C_8-Cycloalkyl-Gruppen, $-CONR^9R^{10}$ (R^9 und R^{10} bedeuten jeweils unabhängig Wasserstoffatome oder C_1-C_6-Alkyl-Gruppen) darstellen, oder wenn R^7 und R^8 benachbart sind, sie eine C_1-C_6-Alkylen-Gruppe bilden können, und m stellt 0 oder 1 dar, R^5 stellt eine C_1-C_6-Alkyl-Gruppe dar, X stellt $-CONR^{13}-$ oder $-SO_2NR^{13}-$ dar (R^{13} stellt Wasserstoff oder eine C_1-C_6-Alkyl-Gruppe dar) und der Ring A kann einen Benzol-Ring oder einen Cyclohexen-Ring bilden.

4. Verbindungen gemäß Anspruch 3, worin R^1, R^2, R^3 und R^4 jeweils unabhängig darstellen: Wasserstoffatome; Halogenatome; C_1-C_{14}-Alkyl-Gruppen mit gegebenenfalls einer oder mehreren C_3-C_{10}-Cycloalkyl-Gruppen; C_1-C_{14}-Alkoxy-Gruppen mit gegebenenfalls einer oder mehreren C_3-C_{10}-Alkyl-Gruppen; oder $-OR^6$ (R^6 stellt eine C_1-C_6-Cycloalkyl-Gruppe mit gegebenenfalls einer oder mehreren C_1-C_6-Alkyl-Gruppen dar); X stellt $-CONR^{13}-$ dar (R^{13} stellt ein Wasserstoffatom dar), Y stellt eine Einfachbindung dar, der Ring A bedeutet einen Cyclohexen-Ring und die gepunktete Linie stellt eine Doppelbindung dar.

5. Verbindung gemäß Anspruch 4, worin R^1, R^2, R^3 und R^4 jeweils unabhängig Wasserstoffatome oder C_1-C_{14}-Alkoxy-Gruppen darstellen und n 2 bedeutet.

6. Pharmazeutische Zusammensetzung, umfassend ein Carbonsäure-Derivat gemäß Anspruch 1 oder eines seiner pharmazeutisch akzeptablen Salze zusammen mit einem pharmazeutisch akzeptablen Träger dafür.

7. Therapeutisches Arzneimittel zur Behandlung von Androgen-abhängigen Krankheiten, umfassend ein Carbonsäure-Derivat gemäß Anspruch 1 oder ein pharmazeutisch akzeptables Salz davon als Wirkstoff zusammen mit einem pharmazeutisch akzeptablen Träger dafür.

8. Therapeutisches Mittel gemäß Anspruch 7, worin die Androgen-abhängige Krankheit benigne Prostatahyperplasie ist.

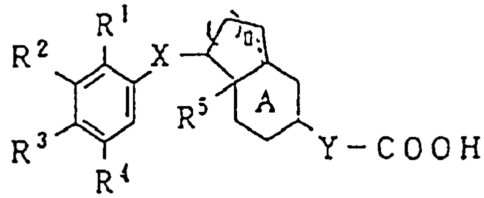
9. Therapeutisches Mittel gemäß Anspruch 7, worin die Androgen-abhängige Krankheit Akne ist.

10. Therapeutisches Mittel gemäß Anspruch 7, worin die Androgen-abhängige Krankheit Seborrhoe ist.

11. Therapeutisches Mittel gemäß Anspruch 7, worin die Androgen-abhängige Krankheit übermäßiger Haarausfall bei Frauen (weiblicher Hirsutismus) ist.

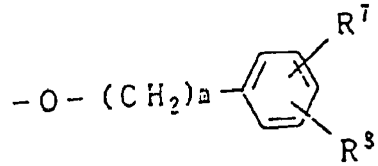
12. Therapeutisches Mittel gemäß Anspruch 7, worin die Androgen-abhängige Krankheit männliche Alopexie ist.

13. Verfahren zur Herstellung von Carbonsäure-Derivaten mit der allgemeinen Formel (I)



(I)

worin R^1, R^2, R^3 und R^4 jeweils unabhängig Wasserstoffatome, Halogenatome, Adamantyl-Gruppen, gegebenenfalls substituierte C_1-C_{14}-Alkyl-Gruppen, gegebenenfalls substituierte C_3-C_{10}-Cycloalkyl-Gruppen, gegebenenfalls substituierte C_1-C_{14}-Alkoxy-Gruppen, gegebenenfalls substituierte heterocyclische Gruppen, $-OR^6$ (R^6 stellt ein Wasserstoffatom, eine Adamantyl-Gruppe, eine gegebenenfalls substituierte C_3-C_{10}-Cycloalkyl-Gruppe oder eine gegebenenfalls substituierte heterocyclische Gruppe dar), oder eine Gruppe mit der Formel:



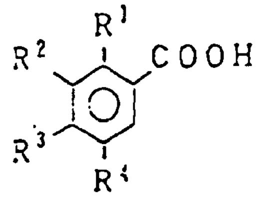
bedeuten, worin R^7 und R^8 jeweils unabhängig Wasserstoffatome, C_1-C_6-Alkyl-Gruppen, C_3-C_8-Cycloalkyl-Gruppen, $-CONR^9R^{10}$ (R^9 und R^{10} bedeuten jeweils unabhängig Wasserstoffatome oder C_1-C_6-Alkyl-Gruppen) darstellen, oder, wenn R^7 und R^8 benachbart sind, sie eine C_1-C_6-Alkylen-Gruppe bilden können, und m 0 oder 1 darstellt, oder wobei zwei benachbarte Substituenten aus R^1, R^2, R^3 und R^4 eine Gruppe mit der Formel:

$$-\underset{R^{12}}{\overset{R^{11}}{\overset{|}{\underset{|}{\mathrm{OCO}}}}}-$$

bilden können, worin R^{11} und R^{12} jeweils unabhängig Wasserstoffatome, C_1-C_6-Alkyl-Gruppen oder C_3-C_8-Cycloalkyl-Gruppen darstellen oder zusammengenommen eine C_2-C_8-Alkylen-Gruppe, eine Gruppe mit der Formel $-OCH_2CH_2O-$ oder eine gegebenenfalls substituierte C_3-C_4-Alkylen-Gruppe bilden können,

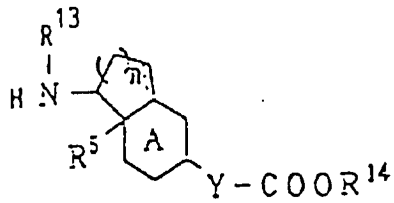
R^5 ein Wasserstoffatom oder eine C_1-C_5-Alkyl-Gruppe darstellt,
X $-CONR^{13}-$ oder $-SO_2NR^{13}-$ darstellt (R^{13} bedeutet ein Wasserstoffatom oder eine C_1-C_6-Alkyl-Gruppe),
Y eine Einfachbindung, $-OCH_2-$ oder $-CH{=}CH-$ bedeutet;
der Ring A einen Benzol-Ring, Cyclohexen-Ring oder Cyclohexadien-Ring bilden kann,
die gepunktete Linie eine Einfachbindung oder eine Doppelbindung darstellt und
n 1 oder 2 darstellt, mit der Maßgabe, daß wenn das Kohlenstoffatom, an das R^5 gebunden ist, eine Doppelbindung aufweist, dann R^5 nicht vorliegt,
umfassend die folgenden Schritte:

Kondensierung von Benzoesäure-Derivaten der allgemeinen Formel (III):



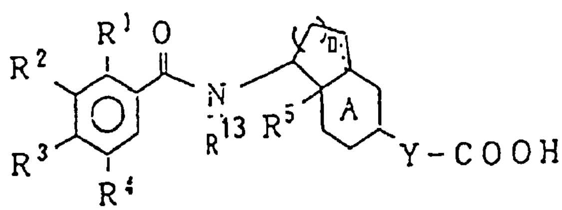
(III)

worin R^1, R^2, R^3 und R^4 wie oben definiert sind, mit Aminosäure-Derivaten der allgemeinen Formel (IV):



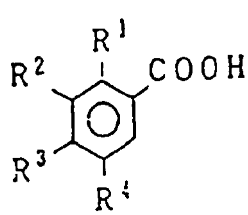
(IV)

worin R^5 und R^{13} wie oben definiert sind und R^{14} eine Alkyl-Gruppe mit 1 bis 5 Kohlenstoffatomen darstellt; Hydrolyse des resultierenden kondensierten Produkts mit einer Alkalie zur Bildung der Zielverbindung (Ia):



(Ia)

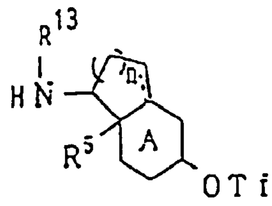
14. Verfahren zur Herstellung von Carbonsäure-Derivaten mit der allgemeinen Formel (I) gemäß Anspruch 13, worin R^1, R^2, R^3, R^4, R^5, n und A dieselbe Bedeutung wie in Anspruch 13 haben, X -CONR^{13} bedeutet, wobei R^{13} wie in Anspruch 13 definiert ist, und Y eine Einfachbindung bedeutet, umfassend die folgenden Schritte:
Kondensierung von Benzoesäure-Derivaten mit der allgemeinen Formel (III):



(III)

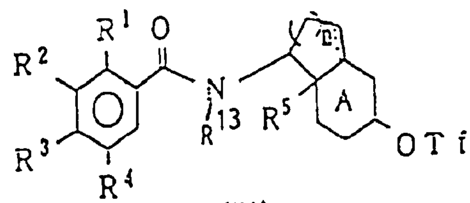
worin R^1, R^2, R^3 und R^4 wie in Anspruch 13 definiert sind,

mit Amin-Derivaten der allgemeinen Formel (V) :



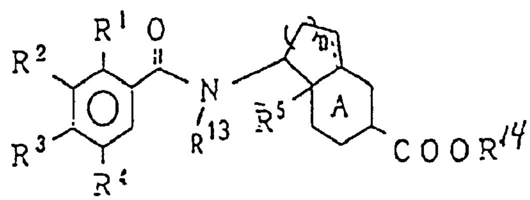
(V)

worin R^5 und R^{13} wie in Anspruch 13 definiert sind und Tf eine Trifluormethansulfonyl-Gruppe bedeutet, zur Bildung einer Verbindung mit der allgemeinen Formel (VI):



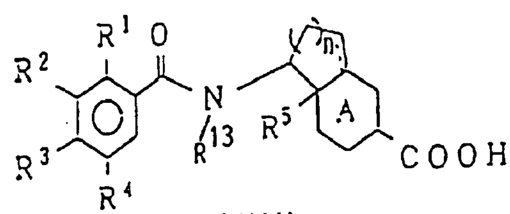
(VI)

Umsetzung der Verbindung der obigen Formel (VI) mit Kohlenmonoxid in Gegenwart einer organischen Base, Trialkylphosphin und Palladium(II) in einem Alkanol-Lösungsmittel (ROH) oder einer Mischung eines Alkanols ($R^{14}OH$) mit Tetrahydrofuran, Ether oder Methylenchlorid, wobei R^{14} eine Alkyl-Gruppe mit 1 bis 5 Kohlenstoffatomen darstellt, zur Bildung des Esters mit der allgemeinen Formel (VII):



(VII)

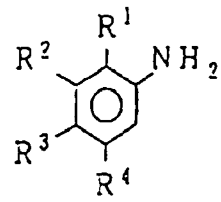
und Hydrolyse des Esters der allgemeinen Formel (VII) mit einer Alkalie zur Bildung der zielverbindung mit der Formel (VIII):



(VIII)

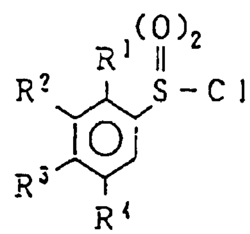
15. Verfahren zur Herstellung von Carbonsäure-Derivaten mit der allgemeinen Formel (I) gemäß Anspruch 13, worin

R^1, R^2, R^3, R^5, n, Y und A dieselbe Bedeutung wie in Anspruch 13 haben und X $-SO_2NR^{13}$ ist, wobei R^{13} wie in Anspruch 13 definiert ist, umfassend die folgenden Schritte:
Umsetzung von Anilin-Derivaten der allgemeinen Formel (IX):



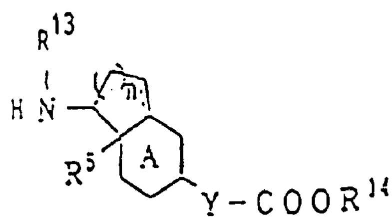
(IX)

worin R^1, R^2, R^3 und R^4 wie in Anspruch 13 definiert sind, mit Natriumnitrit oder Kaliumnitrit zur Bildung eines Diazoniumsalzes, das mit Kupferchlorid und Schwefeldioxid umgesetzt wird, so daß das Sulfonylchlorid-Derivat mit der allgemeinen Formel (X) entsteht:



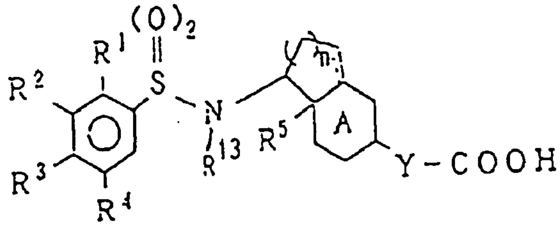
(X)

Umsetzung der Verbindung der allgemeinen Formel (X) mit einer Verbindung der allgemeinen Formel (IV):



(IV)

worin R^5 und R^{13} wie in Anspruch 13 definiert sind und R^{14} eine Alkyl-Gruppe mit 1 bis 5 Kohlenstoffatomen darstellt, in einem halogenierten Lösungsmittel und alkalische Hydrolyse des resultierenden Produkts, so daß die zielverbindung der allgemeinen Formel (XI) erhalten wird:

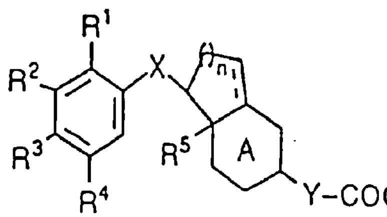


(XI)

16. Verwendung von Carbonsäure-Derivaten mit der allgemeinen Formel (I) gemäß Anspruch 13, worin R^1, R^2, R^3, R^4, R^5, n, Y und A wie in Anspruch 13 definiert sind und X -$CONR^{13}$ ist, wobei R^{13} wie in Anspruch 13 definiert ist, oder von pharmazeutisch akzeptablen Salzen davon zur Herstellung eines Medikaments, das zur Behandlung von Androgen-abhängigen Krankheiten wirksam ist.

17. Verwendung gemäß Anspruch 16, worin die Androgen-abhängige Krankheit dargestellt wird durch benigne Prostatahyperplasie, Akne, Seborrhoe, übermäßigen Haarausfall bei Frauen oder männliche Alopexie.

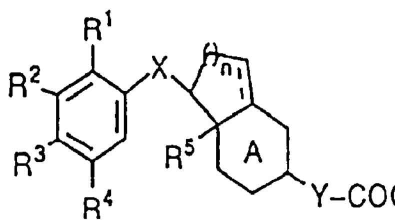
18. Verbindung der Formel:



(I')

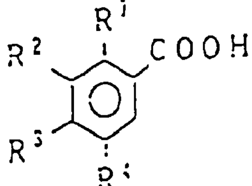
worin R^{14} C_1-C_5-Alkyl ist und R^1, R^2, R^3, R^4, R^5, A, X, Y und n wie in Anspruch 13 definiert sind.

19. Verfahren zur Herstellung von Carbonsäure-Derivaten mit der allgemeinen Formel (I'):



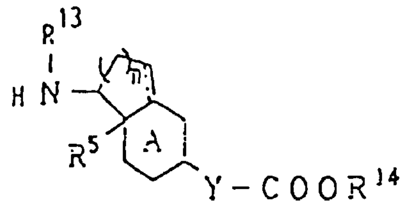
(I')

worin R^{14} C_1-C_5-Alkyl ist und R^1, R^2, R^3, R^4, R^5, A, X, Y und n wie in Anspruch 13 definiert sind, umfassend die folgenden Schritte:
Kondensierung von Benzoesäure-Derivaten mit der allgemeinen Formel (III):



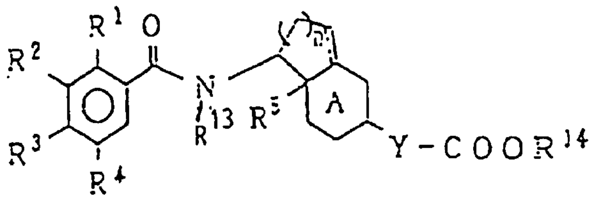
(III)

mit Aminosäure-Derivaten der allgemeinen Formel (IV):



(IV)

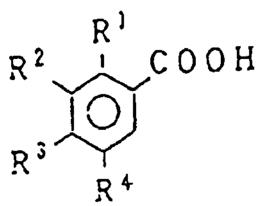
zur Bildung der Zielverbindung (I'a):



(I'a)

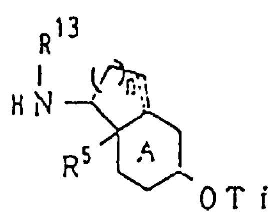
worin R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A, X, Y und n wie oben definiert sind.

20. Verfahren zur Herstellung von Carbonsäure-Derivaten mit der allgemeinen Formel (VII), umfassend die folgenden Schritte:
Kondensierung von Benzoesäure-Derivaten der allgemeinen Formel (III):



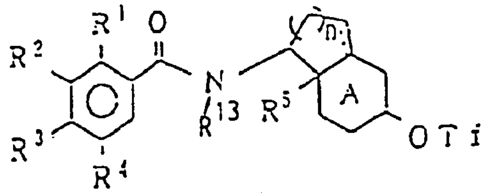
(III)

mit Amin-Derivaten der allgemeinen Formel (V):



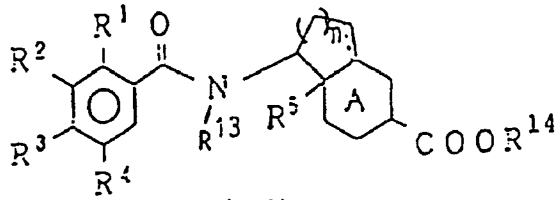
(V)

zur Bildung von Verbindungen der allgemeinen Formel (VI):



(VI)

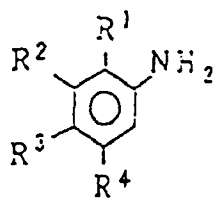
Umsetzung der Verbindung der obigen Formel (VI) mit Kohlenmonoxid in Gegenwart einer organischen Base, Trialkylphosphin und Palladium(II) in einem Alkanol-Lösungsmittel (ROH) oder einer Mischung eines Alkanols ($R^{14}OH$) mit Tetrahydrofuran, Ether oder Methylenchlorid, wobei R^{14} eine Alkyl-Gruppe mit 1 bis 5 Kohlenstoffatomen darstellt, so daß der Ester der allgemeinen Formel (VII) entsteht:



(VII)

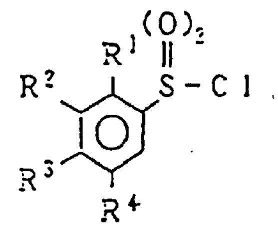
worin Tf eine Trifluormethansulfonyl-Gruppe darstellt und R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A und n wie in Anspruch 19 definiert sind.

21. Verfahren zur Herstellung von Carbonsäure-Derivaten mit der allgemeinen Formel (XI'), umfassend die folgenden Schritte:
Umsetzung von Anilin-Derivaten der allgemeinen Formel (IX) :



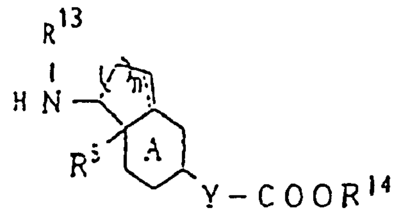
(IX)

mit Natriumnitrit oder Kaliumnitrit zur Bildung eines Diazoniumsalzes, das mit Kupferchlorid und Schwefeldioxid zur Bildung des Sulfonylchlorid-Derivats der allgemeinen Formel (X) umgesetzt wird:



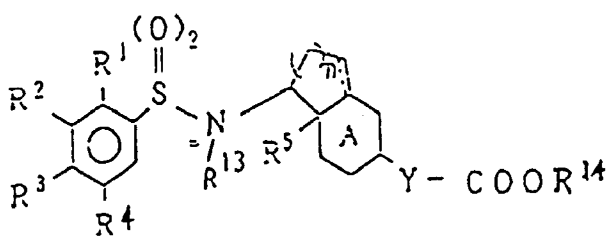
(X)

Umsetzung der Verbindung der allgemeinen Formel (X) mit einer Verbindung der allgemeinen Formel (IV):



(IV)

in einem halogenierten Lösungsmittel zur Bildung der Zielverbindung der allgemeinen Formel (XI'):

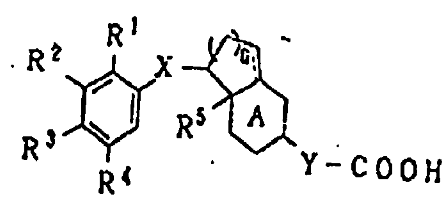


(XI')

worin R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A, Y und n wie in Anspruch 19 definiert sind.

Revendications

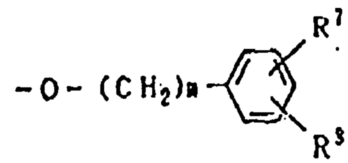
1. Dérivés d'acide carboxylique correspondant à la formule générale suivante (I):



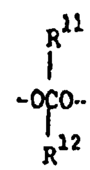
(I)

dans laquelle R^1, R^2, R^3, et R^4 représentent chacun, de manière indépendante, un atome d'hydrogène, un atome d'halogène, un groupe adamantyle, un groupe alkyle en C_1 à C_{14} éventuellement substitué, un groupe cycloalkyle en C_3 à C_{10} éventuellement substitué, un groupe alcoxy en C_1 à C_{14} éventuellement substitué, un

groupe hétérocyclique éventuellement substitué, - un groupe OR^6 (R^6 représentant un atome d'hydrogène, un groupe adamantyle, un groupe cycloalkyle en C_3 à C_{10} éventuellement substitué ou un groupe hétérocyclique éventuellement substitué) ou un groupe de formule:



dans laquelle R^7 et R^8 représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe cycloalkyle en C_3 à C_8, un groupe $CONR^9R^{10}$ (R^9 et R^{10} représentant chacun, de manière indépendante, un atome d'hydrogène ou un groupe alkyle en C_1 à C_6) ou, lorsque R^7 et R^8 sont adjacents, ils peuvent former un groupe alkylène en C_1 à C_5, et m est égal à 0 ou à 1, ou les deux substituants adjacents choisis parmi R^1, R^2, R^3 et R^4 peuvent former un groupe de formule:



dans laquelle R^{11} et R^{12} représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe cycloalkyle en C_3 à C_8 ou ils peuvent former ensemble un groupe alkylène en C_2 à C_8, un groupe de formule $-OCH_2CH_2O-$ ou un groupe alkylène en C_3 ou C_4, éventuellement substitué,

R^5 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_5,

X représente un groupe $-CONR^{13}-$ ou $-SO_2NR^{13}$ (R^{13} représentant un atome d'hydrogène ou un groupe alkyle en C_1 à C_6),

Y représente une simple liaison, - OCH2- ou -CH=CH-,

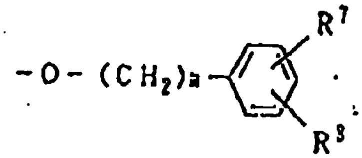
le cycle A peut former un noyau benzène, cyclohexène ou cyclohexadiène,

la ligne pointillée représente une simple ou une double liaison, et

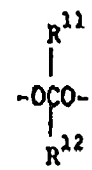
n représente 1 ou 2, sous réserve que, lorsque l'atome de carbone auquel est attaché R^5 possède une double liaison, R^5 n'est pas présent, ou des sels de ceux-ci acceptables sur le plan pharmaceutique.

2. Composé selon la revendication 1, dans lequel R^1, R^2, R^3, et R^4 représentent chacun, de manière indépendante, un atome d'hydrogène, un atome d'halogène, un groupe adamantyle, un groupe alkyle en C_1 à C_{14} portant éventuellement un ou plusieurs substituants choisi parmi des hydrocarbures hétérocycliques à 5 ou 6 chainons contenant 1 ou 2 hétéroatomes choisis entre un atome d'oxygène, un atome de soufre et un atome d'azote, un groupe cycloalkyle en C_3 à C_{10} et un groupe adamantyle; un groupe cycloalkyle en C_3 à C_{10} possédant éventuellement un ou plusieurs groupes alkyle en C_1 à C_6; un groupe alcoxy en C_1 à C_{14} possédant éventuellement deux ou plusieurs groupes phényle ou un ou plusieurs substituants choisi parmi des hydrocarbures hétérocycliques à 5 ou 6 chainons contenant 1 ou 2 hétéro atomes choisis entre un atome d'oxygène, un atome de soufre et un atome d'azote, un groupe cycloalkyle en C_3 à C_{10} et un groupe adamantyle; un groupe hétérocyclique à 5 ou 6 chainons contenant 1 ou 2 hétéro atomes choisis entre un atome d'oxygène, un atome de soufre et un atome d'azote et possédant éventuellement un ou plusieurs groupes alkyle en C_1 à C_6; un groupe $-OR^6$ [R^6 représente un atome d'hydrogène; un groupe adamantyle; un groupe cycloalkyle en C_3 à C_{10} portant éventuellement un ou plusieurs groupes alkyle en C_1 à C_6; ou un groupe hétérocyclique à 5 ou 6 chainons contenant 1 ou 2 hétéro atomes choisis entre un atome d'oxygène, un atome de soufre et un atome d'azote et possédant éventuellement un ou plusieurs

substituants choisis parmi un groupe alkyle en C_1 à C_6 et un groupe acyle en C_2 à C_6]; ou un groupe de formule:

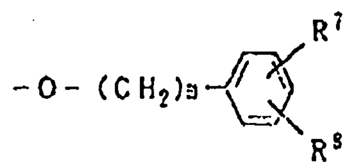


dans laquelle R^7 et R^8 représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe cycloalkyle en C_3 à C_8, un groupe -$CONR^9R^{10}$ (R^9 et R^{10} représentent chacun de manière indépendante un atome d'hydrogène ou un groupe alkyle en C_1 à C_6) ou, lorsque R^7 et R^8 sont adjacents, ils peuvent former un groupe alkylène en C_1 à C_6, et m est égal à 0 ou à 1, ou les deux substituants adjacents sélectionnés parmi R^1, R^2, R^3 et R^4 peuvent former un groupe de formule:



dans laquelle R^{11} et R^{12} représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe cycloalkyle en C_3 à C_8 ou ils peuvent former ensemble un groupe alkylène en C_2 à C_8, un groupe de formule -OCH_2CH_2O-; ou un groupe alkylène en C_3 ou C_4 possédant éventuellement un ou plusieurs substituants choisis entre un groupe alkyle en C_1 à C_6 et un groupe cycloalkyle en C_3 à C_8.

3. Composé selon la revendication 2, dans lequel R^1, R^2, R^3, et R^4 représentent chacun, de manière indépendante, un atome d'hydrogène, un atome d'halogène, un groupe alkyle en C_1 à C_{14} portant éventuellement un ou plusieurs substituants choisi parmi un groupe hétérocyclique à 5 ou 6 chainons contenant 1 ou 2 hétéroatomes choisis entre un atome d'oxygène, un atome de soufre, un atome d'azote, un groupe cycloalkyle en C_3 à C_{10}; un groupe alcoxy en C_1 à C_{14} possédant éventuellement deux ou plusieurs groupes phényle ou un ou plusieurs groupes cycloalkyle en C_3 à C_{10}; un groupe -OR^6 (R^6 représentant un groupe cycloalkyle en C_3 à C_{10} portant éventuellement un ou plusieurs groupes alkyle en C_1 à C_6; ou un groupe hétérocyclique à 5 ou 6 chainons contenant 1 ou 2 hétéroatomes choisis entre un atome d'oxygène, un atome de soufre et un atome d'azote et possédant éventuellement un ou plusieurs groupes alkyle en C_1 à C_6] ou un groupe de formule:



dans laquelle R^7 et R^8 représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe cycloalkyle en C_3 à C_8, un groupe -$CONR^9R^{10}$ (R^9 et R^{10} représentant chacun de manière indépendante un atome d'hydrogène ou un groupe alkyle en C_1 à C_6) ou, lorsque R^7 et R^8 sont adjacents, ils peuvent former un groupe alkylène en C_1 à C_6 et m est égal à 0 ou à 1, R^5 représente un groupe alkyle en C_1 à C_6, X représente un groupe -$CONR^{13}$ ou -SO_2NR^{13} (R^{13} représentant un atome d'hydrogène ou un groupe alkyle en C_1 à C_6), et un cycle A peut former un noyau benzène ou cyclohexene.

4. Composé selon la revendication 3, dans lequel R^1, R^2, R^3, et R^4 représentent chacun, de manière indépendante, un atome d'hydrogène; un atome d'halogène; un groupe alkyle en C_1 à C_{14} portant éventuellement un ou plusieurs groupes cycloalkyle en C_3 à C_{10}; un groupe alcoxy en C_1 à C_{14} possédant éventuellement un ou plusieurs groupes alkyle en C_3 à C_{10}; ou un groupe -OR^6 (R^6 représentant un groupe cycloalkyle en C_1 à C_6 portant éventuellement

un ou plusieurs groupes alkyle en C_1 à C_6), X représente un groupe -CONR^{13} (R^{13} représentant un atome d'hydrogène), Y représente une simple liaison, A représente un noyau cyclohexène, et la ligne pointillée représente une double liaison.

5. Composé selon la revendication 4, dans lequel R^1, R^2, R^3, et R^4 représentent chacun, de manière indépendante, un atome d'hydrogène ou un groupe alcoxy en C_1 à C_{14} et n est égal à 2.

6. Composition pharmaceutique comprenant un dérivé d'acide carboxylique selon la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique accompagné d'un support acceptable sur le plan pharmaceutique.

7. Produit pharmaceutique thérapeutique destiné au traitement des maladies androgénodépendantes comprenant un dérivé d'acide carboxylique selon la revendication 1 ou un sel de celui-ci acceptable sur le plan pharmaceutique en tant que principe actif accompagné d'un support acceptable sur le plan pharmaceutique.

8. Produit pharmaceutique thérapeutique selon la revendication 7, dans lequel la maladie androgénodépendante est une hyperplasie de la prostate bénigne.

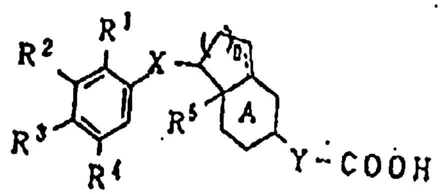
9. Produit pharmaceutique thérapeutique selon la revendication 7, dans lequel la maladie androgénodépendante est une acné.

10. Produit pharmaceutique thérapeutique selon la revendication 7, dans lequel la maladie androgénodépendante est une seborrhée.

11. Produit pharmaceutique thérapeutique selon la revendication 7, dans lequel la maladie androgénodépendante est l'hirsutisme féminin.

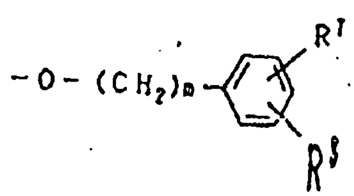
12. Produit pharmaceutique thérapeutique selon la revendication 7, dans lequel la maladie androgènodépendante est l'alopécie masculine.

13. Procédé de préparation de dérivés d'acide carboxylique de formule générale (I):



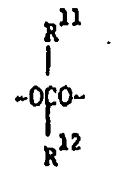
(I)

dans laquelle R^1, R^2, R^3, et R^4 représentent chacun, de manière indépendante, un atome d'hydrogène, un atome d'halogène, un groupe adamantyle, un groupe alkyle en C_1 à C_{14} éventuellement substitué, un groupe cycloalkyle en C_3 à C_{10} éventuellement substitué, un groupe alcoxy en C_1 à C_{14} éventuellement substitué, un groupe hétérocyclique éventuellement substitué, un groupe -OR^6 (R^6 représentant un atome d'hydrogène, un groupe adamantyle, un groupe cycloalkyle en C_3 à C_{10} éventuellement substitué ou un groupe hétérocyclique éventuellement substitué) ou un groupe de formule:



dans laquelle R^7 et R^8 représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe cycloalkyle en C_3 à C_8, un groupe -CONR^{9}R^{10} (R^9 et R^{10} représentant chacun de

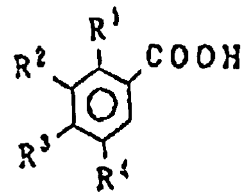
manière indépendante un atome d'hydrogène ou un groupe alkyle en C_1 à C_6) ou, lorsque R^7 et R^8 sont adjacents, ils peuvent former un groupe alkylène en C_1 à C_6, et m est égal à 0 ou à 1, ou les deux substituants adjacents choisis parmi R^1, R^2, R^3 et R^4 peuvent former un groupe de formule:



dans laquelle R^{11} et R^{12} représentent chacun, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1 à C_6, un groupe cycloalkyle en C_3 à C_8 ou ils peuvent former ensemble un groupe alkylène en C_2 à C_8, un groupe de formule $-OCH_2CH_2O-$ ou un groupe alkylène en C_3 ou C_4, éventuellement substitué,

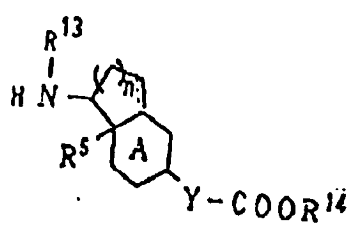
R^5 représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_5,
X représente un groupe $-CONR^{13}-$ ou $-SO_2NR^{13}$ (R^{13} représentant un atome d'hydrogène ou un groupe alkyle en C_1 à C_6),
Y représente une simple liaison, $-OCH_2-$ ou $-CH=CH-$,

le cycle A peut former un noyau benzène, cyclohexène ou cyclohexadiène,
la ligne pointillée représente une simple ou une double liaison, et
n représente 1 ou 2, sous réserve que, lorsque l'atome de carbone auquel est attaché R^5 possède une double liaison, R^5 ne soit pas présent, lequel procédé comprend les étapes suivantes:
la condensation de dérivés d'acide benzoïque de formule générale (III):



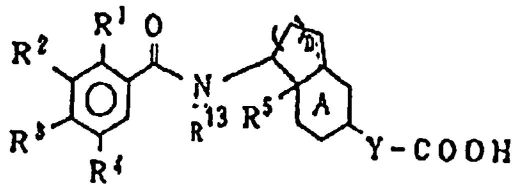
(III)

dans laquelle R^1, R^2, R^3, et R^4 sont tels que précédemment définis,
avec des dérivés d'acide aminé de formule générale (IV):



(IV)

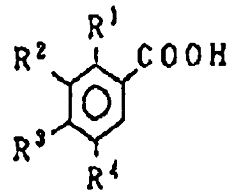
dans laquelle R^5, et R^{13} sont tels que précédemment définis et R^{14} représente un groupe alkyle possédant de 1 à 5 atomes de carbone;
l'hydrolyse du produit condensé ainsi obtenu avec un alcali de façon à donner le composé recherché (Ia):



(I a)

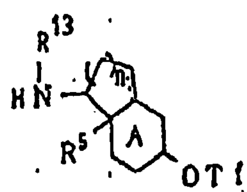
14. Procédé de préparation de dérivés d'acide carboxylique de formule générale (I), comme défini à la revendication 13, où R^1, R^2, R^3, R^4, R^5, n et A ont la même signification que défini à la revendication 13, X représente un groupe $-CONR^{13}$, où R^{13} est tel que défini à la revendication 13, et Y représente une simple liaison, lequel procédé comprend les étapes suivantes:

la condensation de dérivés d'acide benzoïque de formule générale (III):



(III)

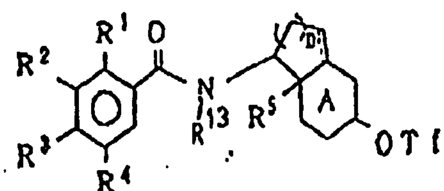
dans laquelle R^1, R^2, R^3, et R^4 sont tels que définis à la revendication 13,
avec des dérivés aminés de formule générale (V):



(V)

dans laquelle R^5 et R^{13} sont tels que définis à la revendication 13 et Tf représente un groupe trifluorométhanesulfonyle,

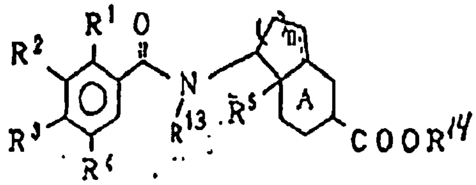
pour donner le composé de formule générale (VI):



(VI)

la réaction du composé correspondant à la formule précédente (VI) avec du monoxyde de carbone en présence d'une base organique, de trialkylphosphine et de palladium (II) dans un solvant à base d'alcanol ou dans

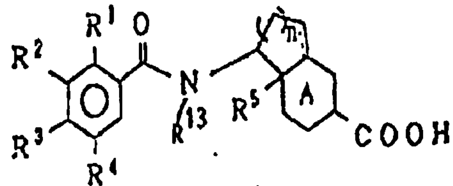
un mélange d'alcanol ($R^{14}OH$) avec du tétrahydrofurane, de l'éther ou du chlorure de méthylène, dans lequel R^{14} représente un groupe alkyle de 1 à 5 atomes de carbone, pour donner l'ester de formule générale (VII):



(VII)

et

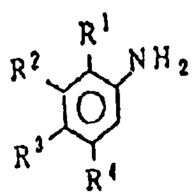
l'hydrolyse de l'ester de formule générale (VII) avec un alcali de façon à obtenir le composé recherché de formule (VIII):



(VIII)

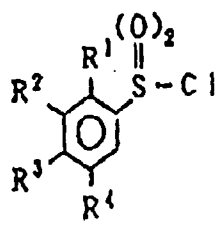
15. Procédé de préparation de dérivés d'acide carboxylique de formule générale (I), comme défini à la revendication 13, où R^1, R^2, R^3, R^4, R^5, n, Y et A ont la même signification que défini à la revendication 13 et X représente un groupe $-SO_2NR^{13}$, où R^{13} est tel que défini à la revendication 13, lequel procédé comprend les étapes suivantes:

la réaction de dérivés de l'aniline de formule générale (IX):



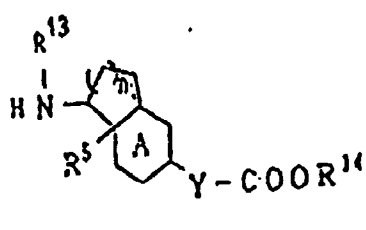
(IX)

dans laquelle R^1, R^2, R^3, et R^4 sont tels que définis à la revendication 13, avec du nitrite de sodium ou du nitrite de potassium pour donner un sel de diazonium, qui est soumis à une réaction avec du chlorure cuprique et du dioxyde de soufre de façon à obtenir un dérivé du chlorure de sulfonyle de formule générale (X):



(X)

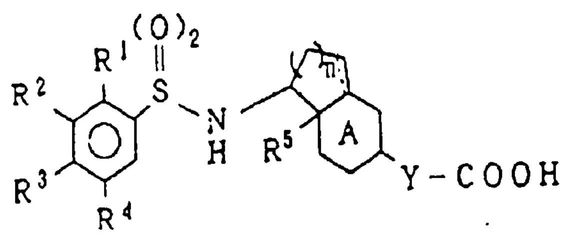
la réaction du composé de la formule générale (X) avec un composé de formule générale (IV):



(IV)

dans laquelle R^5 et R^{13} sont tels que définis à la revendication 13 et R^{14} représente un groupe alkyle possédant de 1 à 5 atomes de carbone,

dans un solvant de type halogène et l'exposition du produit ainsi obtenu à une hydrolyse par un alcali de façon à obtenir le composé recherché de formule générale (XI):

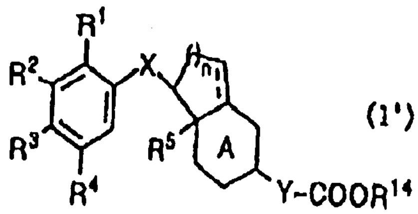


(XI)

16. Utilisation de dérivés d'acide carboxylique de formule générale (I), comme défini à la revendication 13, où R^1, R^2, R^3, R^4, R^5, n, Y et A sont tels que définis à la revendication 13, X représente un groupe -$CONR^{13}$, dans lequel R^{13} est tel que défini à la revendication 13, ou d'un sel de ceux-ci acceptable sur le plan pharmaceutique pour préparer un médicament efficace pour le traitement des maladies androgénodépendantes.

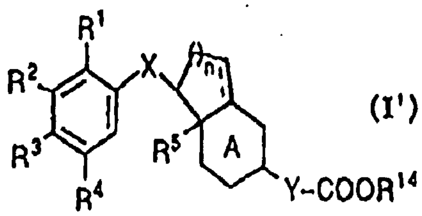
17. Utilisation selon la revendication 16, dans laquelle la maladie androgénodépendante est une hyperplasie prostatique bénigne, une acnée, une séborrée, l'hirsutisme féminin ou l'alopécie masculine.

18. Composé de formule (I'), dans laquelle R^{14} est un groupe alkyle en C_1 à C_5, R^1, R^2, R^3, R^4, R^5, A, X, Y et m sont tels que définis à la revendication 13.



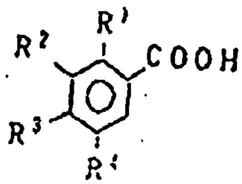
(I')

19. Procédé de préparation de dérivés d'acide carboxylique de formule générale (I'),



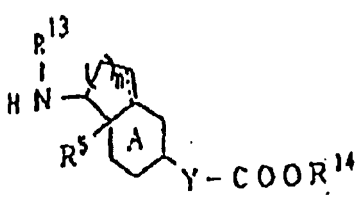
(I')

dans laquelle R^{14} est un groupe alkyle en C_1 à C_5, R^1, R^2, R^3, R^4, R^5, A, X, Y et m sont tels que définis à la revendication 13, comprenant les étapes suivantes: la condensation de dérivés d'acide benzoïque de formule générale (III):



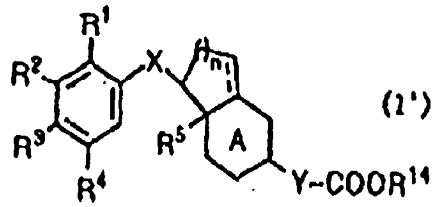
(III)

avec des dérivés d'acide aminé de formule générale (IV):



(IV)

de façon à obtenir le composé recherché (I'a)

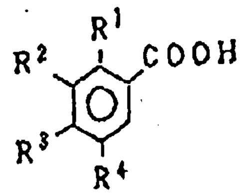


(1')

dans laquelle R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A, X, Y et m sont tels que précédemment définis.

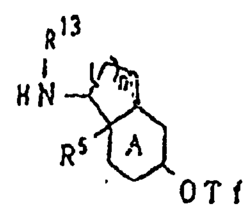
20. Procédé de préparation de dérivés d'acide carboxylique de formule générale (VII), comprenant les étapes suivantes:

la condensation de dérivés d'acide benzoïque de formule générale (III):



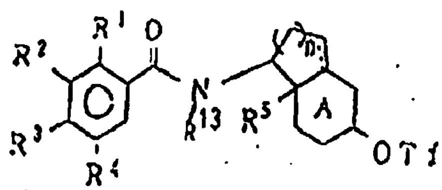
(III)

avec des dérivés aminés de formule générale (V):



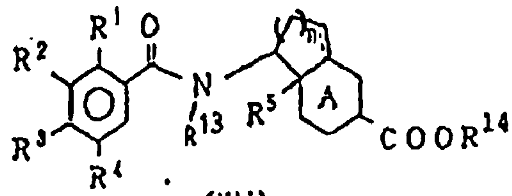
(V)

de façon à obtenir le composé de formule générale (VI):



(VI)

la réaction du composé de la formule (VI) précédente avec du monoxyde de carbone en présence d'une base organique, de trialkylphosphine et de palladium (II) dans un solvant à base d'alcanol (ROH) ou dans un mélange d'alcanol ($R^{14}OH$) avec du tétrahydrofuranne, de l'éther ou du chlorure de méthylène, où R^{14} représente un groupe alkyle de 1 à 5 atomes de carbone, pour donner l'ester de formule générale (VII):

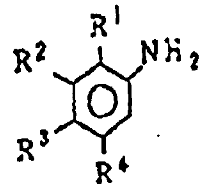


(VII)

où Tf représente un groupe trifluorométhane sulfonyle et R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A, et n sont tels que définis à la revendication 19.

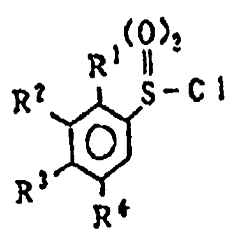
21. Procédé de préparation de dérivés d'acide carboxylique de formule générale (XI'), comprenant les étapes suivantes:

la réaction de dérivés de l'aniline de formule générale (IX)



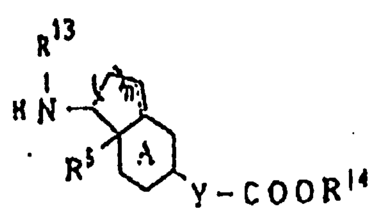
(IX)

avec du nitrite de sodium ou du nitrite de potassium pour donner un sel de diazonium, qui est soumis à une réaction avec du chlorure cuprique et du dioxyde de soufre de façon à obtenir un dérivé du chlorure de sulfonyle de formule générale (X):



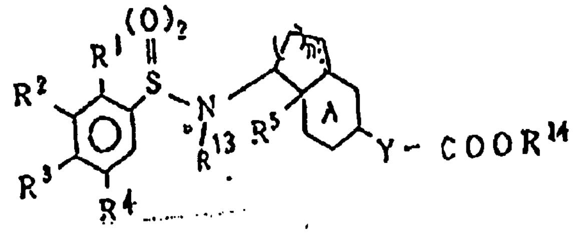
(X)

la réaction du composé de la formule générale (X) avec un composé de formule générale (IV):



(IV)

dans un solvant de type halogéné de façon à obtenir le composé recherché de formule générale (XI)



(XI')

dans laquelle R^1, R^2, R^3, R^4, R^5, R^{13}, R^{14}, A,Y et n sont tels que définis à la revendication 19.

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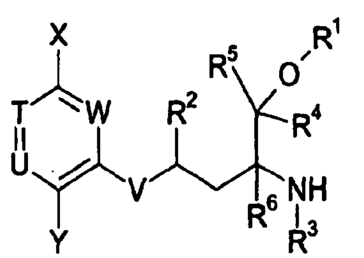
(54) Title: NOVEL ARYLHETEROALKYLAMINE DERIVATIVES



(I)

(57) Abstract: There are provided novel compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, T, U, X, Y, V and W are as defined in the specification, and pharmaceutically acceptable salts thereof, and enantiomers and racemates thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of nitric oxide synthase and are thereby particularly useful in the treatment or prophylaxis of inflammatory disease and pain.

NOVEL COMPOUNDS

Field of the Invention

The present invention relates to novel arylheteroalkylamine derivatives, processes for their preparation, compositions containing them and their use in therapy.

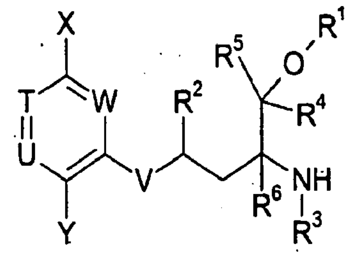
Background of the Invention

Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been particularly implicated in the pathogenesis of inflammatory diseases. Regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states (J. E. Macdonald, *Ann. Rep. Med. Chem.*, 1996, **31**, 221 - 230).

Considerable effort has been expended in efforts to identify compounds that act as specific inhibitors of one or more isoforms of the enzyme nitric oxide synthase. The use of such compounds in therapy has also been widely claimed.

Disclosure of the invention

According to the present invention, there is provided a compound of formula (I)



(I)

wherein:

X represents H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NH_2, $NHCH_3$, $N(CH_3)_2$, NO_2, CH_2OH, CHO, $COCH_3$ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

Y represents C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO_2, CH_2OH, CHO, $COCH_3$ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

T, U and W independently represent CR^7 or N; and each R^7 group independently represents H, F or CH_3; and when T represents CR^7, the group R^7 may additionally represent OH, Cl, Br, CN, CH_2OH, NO_2, NHR^{13}, OR^{14} or OSO_2CH_3;

V represents O or $S(O)_n$;

n represents an integer 0, 1 or 2;

R^1 represents H or Me.

R^2 represents C1 to 4 alkyl, C2 to 4 alkenyl, C2 to 4 alkynyl, C3 to 6 cycloalkyl or a 4 to 8 membered saturated heterocyclic ring incorporating one heteroatom selected from O, S and N; any of said groups being optionally further substituted by C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkylthio, C3 to 6 cycloalkyl, halogen or phenyl; said phenyl group being optionally

further substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3, OCF_3, CN or NO_2;

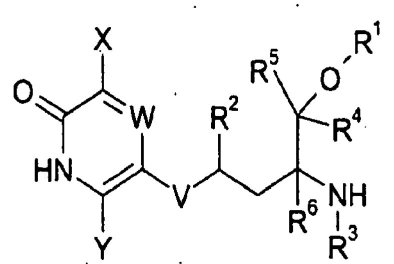
or R^2 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, NO_2 or NR^9R^{10}; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

R^3 represents H, C1 to 4 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally substituted by C1 to 4 alkoxy, halogen, hydroxy, $NR^{11}R^{12}$, phenyl or a five or six membered aromatic or saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally further substituted by halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3, OCF_3, CN or NO_2.

R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently represent H or C1 to 4 alkyl;

or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

It will be recognised that compounds of formula (I) wherein U represents N and T represents CR^7 and R^7 represents OH may exist in the alternative tautomeric form (Ia):



(Ia)

It is to be understood that all such possible tautomeric forms and mixtures thereof are included within the scope of the invention.

In one embodiment, X and Y independently represent C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO_2, CHO, $COCH_3$ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms; and T, U and W independently represent CR^7 or N; and each R^7 group independently represents H, F or CH_3.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers and racemates have the advantage that they are inhibitors of the enzyme nitric oxide synthase (NOS). In particular, the compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers and racemates have the advantage that they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase (iNOS).

The invention further provides a process for the preparation of compounds of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

According to the invention there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof, for use as a medicament.

Another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

A more particular aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

According to the invention, there is also provided a method of treating, or reducing the risk of, diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

More particularly, there is also provided a method of treating, or reducing the risk of, inflammatory disease in a person suffering from or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance; particularly in combination with a cyclooxygenase inhibitor; more particularly in combination with a selective inhibitor of the inducible isoform of cyclooxygenase (COX-2). Thus, in a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in combination with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and inflammatory related disorders. And there is also provided a method of treating, or reducing the risk of, inflammation, inflammatory disease and inflammatory related disorders in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof in combination with a COX-2 inhibitor.

In one embodiment, V represents $S(O)_n$ and n represents 0.

In another embodiment, V represents O.

In another embodiment, X and Y independently represent Br, Cl, CH_3, CH_2F, CHF_2, CF_3, OCH_3 or CN. In yet another embodiment Y represents CN.

In one embodiment, R^1 represents H.

In another embodiment, R^2 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N. In a further embodiment, R^2 represents phenyl, pyridyl, isoxazolyl, isothiazolyl or thiazolyl. In a yet further embodiment, R^2 represents phenyl.

In one embodiment, R^3 represents H.

In another embodiment R^4, R^5 and R^6 each represent H.

In another embodiment, T, U and W independently represent N, CH or CF. In another embodiment U represents N or CH. In yet another embodiment W represents N or CH.

In one embodiment, each of T, U and W represents CR^7.

In one embodiment, one of T, U and W represents N and the other two represent CR^7.

In a particular embodiment, the compounds of formula (I) have the (1R, 3S) absolute stereochemistry.

In one particular aspect the invention relates to compounds of formula (I) wherein V represents O or S; X and Y independently represent Br, Cl, CH_3, CH_2F, CHF_2, CF_3, OCH_3 or CN; R^1, R^3, R^4, R^5 and R^6 each represent H; R^2 represents phenyl, pyridyl, isoxazolyl, isothiazolyl or thiazolyl; T represents N, CH or CF; U represents N or CH; W

represents N or CH; and the compounds have the (1R, 3S) absolute configuration; and pharmaceutically acceptable salts thereof.

In another particular aspect the invention relates to compounds of formula (I) wherein V represents O or S; X and Y independently represent Br, Cl, CH_3, CH_2F, CHF_2, CF_3, OCH_3 or CN; R^1, R^3, R^4, R^5 and R^6 each represent H; R^2 represents phenyl, pyridyl, isoxazolyl, isothiazolyl or thiazolyl; one of T, U and W represents N and the other two represent CR^7; and the compounds have the (1R, 3S) absolute configuration; and pharmaceutically acceptable salts thereof.

Particular compounds of the invention include:

2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(3S)-3-amino-4-hydroxy-1-(3-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethyl)-3-pyridinecarbonitrile;

2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(fluoromethyl)-3-pyridinecarbonitrile;

2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(3-pyridinyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-isothiazolyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

4-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

4-[[(1R,3R)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

4-[[(1S,3R)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

4-[[(1S,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethoxy)-3-pyridinecarbonitrile;

2-[[(1R,3R)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;

4-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-($^{2}H_3$)methoxy-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-ethyl-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(1-methylethyl)-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinemethanol;

6-acetyl-2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(hydroxymethyl)-3-pyridinecarbonitrile;

2-[[(1R, 3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile;

(β^1S,δ^1R)-β-amino-δ-[(2,5-dichloro-4-pyridinyl)thiobenzenebutanol];

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-fluoro-6-methoxy-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(dimethylamino)-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(methylamino)-3-pyridinecarbonitrile;

(β^1S,δ^1R)-β-amino-δ-[(5-bromo-2-methoxy-4-pyridinyl)thio]-benzenebutanol;

(β^1S,δ^1R)-β-amino-δ-[(5-chloro-2-methoxy-4-pyridinyl)thio]-benzenebutanol;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-ethoxy-3-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-1,6-dihydro-5-methyl-6-oxo-2-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-2-pyridinecarbonitrile;

6-amino-4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-methyl-2-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-1-(2-fluorophenyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-1-(4-fluorophenyl)-4-hydroxybutyl]oxy]-6-trifluoromethyl-3-pyridinecarbonitrile;

2(2S)-amino-4 (4R)-(3-fluorophenyl)-4-[(4-methoxy-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(4-chloro-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(5-amino-4-chloro-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(4-hydroxymethyl)-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(4-fluoro-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(3,5-dichloro-2-pyridyl)thio]butan-1-ol;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-chlorobenzonitrile;

4-chloro-2-[[(1R,3S)-3-(ethylamino)-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-benzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]oxy]-5-fluoro-benzonitrile;

2-[[(1R,3S)-3-amino-4-methoxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-4-methyl-1-phenylpentyl]oxy]-4-chloro-5-fluoro benzonitrile;

2-[[(1S,3S)-3-amino-4-hydroxy-1-propylbutyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1S)-1-[(2S)-2-amino-3-hydroxypropyl]pentyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(1S,3S)-3-amino-4-hydroxy-1-(2-methylpropyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(3S)-3-amino-4-hydroxy-1-(5-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(3S)-3-amino-4-hydroxy-1-(5-isoxazolyl)butyl]oxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile;

2-[[3-(3S)-amino-4-hydroxy-1-(1R)-(2-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[3-(3S)-amino-4-hydroxy-1(1R)-(3-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-(trifluoromethyl)benzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-pyrimidyl)butyl]thio]-4-chlorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(3-pyridyl)butyl]thio]-4-bromobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-6-methyl-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-1-(3-fluoro-2-thienyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-1-(4-chloro-5-thiazolyl)-4-hydroxybutyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-nitrobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-3-pyridinecarbonitrile;

β-amino-δ-[(4-amino-2-nitrophenyl)thio]-(β^1S,δ^1R)-benzenebutanol;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-bromo-benzonitrile;

and pharmaceutically acceptable salts, enantiomers or racemates thereof.

Unless otherwise indicated, the term "C1 to 4 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

Unless otherwise indicated, the term "C3 to 6 cycloalkyl" referred to herein denotes a cycloalkyl group having from 3 to 6 carbon atoms. Examples of such groups include cyclopropyl, cyclopentyl and cyclohexyl.

Unless otherwise indicated, the term "C2 to 4 alkenyl" referred to herein denotes a straight or branched chain alkyl group having from 2 to 4 carbon atoms incorporating at least one carbon-carbon double bond. Examples of such groups include ethenyl, propenyl and butenyl.

Unless otherwise indicated, the term "C2 to 4 alkynyl" referred to herein denotes a straight or branched chain alkyl group having from 2 to 4 carbon atoms incorporating at least one carbon-carbon triple bond. Examples of such groups include ethynyl, propynyl, and butynyl.

Unless otherwise indicated, the term "C1 to 4 alkoxy" referred to herein denotes a straight or branched chain alkoxy group having from 1 to 4 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy.

The term "C1 to 4 alkylthio" is to be interpreted analogously.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluoro, chloro, bromo and iodo.

Examples of a 4 to 8 membered saturated azacyclic ring optionally incorporating one further heteroatom selected from O, S or N include pyrrolidine, piperidine, piperazine, morpholine and perhydroazepine.

Examples of a 4 to 8 membered saturated heterocyclic ring incorporating one heteroatom selected from O, S or N include pyrrolidine, piperidine, tetrahydrofuran and perhydroazepine.

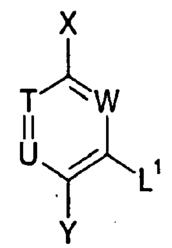
Examples of a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N include furan, thiophene, pyridine, thiazole, imidazole, oxazole, triazole, oxadiazole, thiadiazole and pyrimidine.

Examples of a five or six membered saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N include pyrrolidine, tetrahydrofuran, piperidine and piperazine.

Examples of a "C1 to 4 alkyl or C1 to 4 alkoxy optionally further substituted by one or more fluorine atoms" include CH_2F, CHF_2, CF_3, CF_3CF_2, CF_3CH_2, CH_2FCH_2, CH_3CF_2, $CF_3CH_2CH_2$, OCF_3 and OCH_2CF_3.

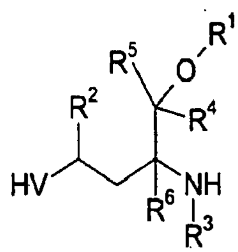
According to the invention, we further provide a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof which comprises:

(a) reaction of a compound of formula (II)



(II)

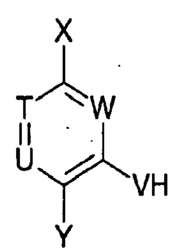
wherein T, U, X, Y and W are as defined in formula (I) and L^1 represents a leaving group, with a compound of formula (III)



(III)

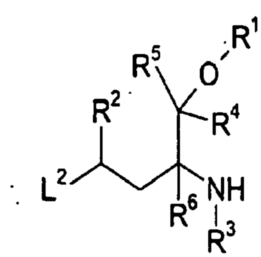
wherein R^1, R^2, R^3, R^4, R^5, R^6 and V are as defined in formula (I); or

(b) reaction of a compound of formula (IV)



(IV)

wherein T, U, W, X, Y and V are as defined in formula (I), with a compound of formula (V)



(V)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in formula (I) and L^2 is a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a), the reaction is performed by treating a nucleophile of formula (III) with an electrophile of formula (II) in an inert solvent. Suitable leaving groups L^1 include sulphonates and halides, particularly fluoride or chloride. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or caesium carbonate. Suitable organic solvents are those such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran, acetonitrile and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

In process (b), the reactants (IV) and (V) are coupled together in a suitable inert solvent such as tetrahydrofuran using, for example, Mitsunobu conditions. Thus, for example, the reactants are treated with a phosphine derivative and an azo derivative at a suitable temperature, generally between 0 °C and the boiling point of the solvent. Suitable phosphine derivatives include triphenylphosphine and tributylphosphine. Suitable azo derivatives include diethyl azodicarboxylate, diisopropyl azodicarboxylate and 1,1'-(azodicarbonyl)dipiperidine. Suitable leaving groups L^2 include hydroxy.

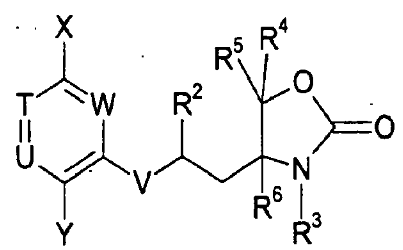
Alternatively in process (b), the reaction is performed by treating a nucleophile of formula (IV) with an electrophile of formula (V) in an inert solvent. Suitable leaving groups L^2 include sulphonates and halides, particularly chloride or bromide. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or caesium carbonate. Suitable organic solvents are those such as N,N-dimethylformamide,

N-methyl-2-pyrrolidinone, tetrahydrofuran and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

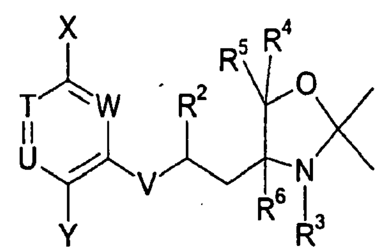
It will be apparent to a person skilled in the art that in the above processes it may be desirable or necessary to protect an amine or hydroxyl or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found by reference to the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

In one preferred embodiment, amine groups are protected as carbamate derivatives, for example, as t-butyloxycarbamates.

In another particularly preferred embodiment, the amine and hydroxyl groups of compounds wherein R^1 represents hydrogen are protected simultaneously as a cyclic carbamate, such as in formula (VI), or as a cyclic hemi-aminal as in formula (VII).



(VI)



(VII)

Specific examples of the use of protecting groups are given in the Examples section.

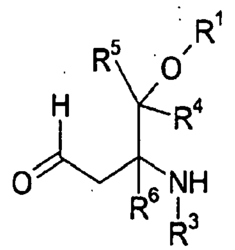
The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from

hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

Salts of compounds of formula (I) may be formed by reacting the free base, or a salt, enantiomer or racemate thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, for example, water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed *in vacuo* or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

Certain novel intermediates of formulae (III), (V), (VI) and (VII) form another aspect of the invention.

Compounds of formula (III) may be prepared by reaction of a compound of formula (VIII)

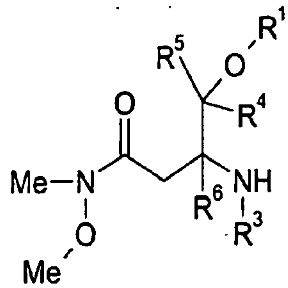


(VIII)

wherein R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I),

with an organometallic derivative, R^2—M, wherein R^2 is as defined in formula (I) and M represents a metallic residue such as lithium or magnesium-halide. The resulting compound of formula (III) wherein V represents oxygen may then be subsequently converted into compounds of formula (III) wherein V represents sulphur.

Alternatively, compounds of formula (III) may be prepared by reaction of an amide of formula (IX)



(IX)

wherein R^1, R^3, R^4, R^5 and R^6 are as defined in formula (I), with an organometallic derivative, R^2— M, wherein R^2 is as defined in formula (I) and M represents a metallic residue such as lithium or magnesium-halide, followed by reduction of the resulting ketone to the corresponding alcohol (III).

Compounds of formulae (II), (IV), (VIII) and (IX) are either known or may be prepared by conventional methods that will be readily apparent to the man skilled in the art.

Intermediate compounds may be used as such or in protected form. Protecting groups and details of processes for their removal may be found by reference to the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The compounds of formula I may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

The compounds of formula (I), and their pharmaceutically acceptable salts, enantiomers and racemates, are useful because they possess pharmacological activity in animals. In particular,

the compounds are active as inhibitors of the enzyme nitric oxide synthase. More particularly, they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase and as such are predicted to be useful in therapy, for example, as anti-inflammatory agents. They may also have utility as inhibitors of the neuronal isoform of the enzyme nitric oxide synthase.

The compounds and their pharmaceutically acceptable salts, enantiomers and racemates are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part. In particular, the compounds are indicated for use in the treatment of inflammatory conditions in mammals including man.

Conditions that may be specifically mentioned are:
osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;
eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;
inflammatory eye conditions including uveitis, glaucoma and conjunctivitis;
lung disorders in which inflammation is involved, for example, asthma, bronchitis, chronic obstructive pulmonary disease, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome;
bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain, meningitis and pancreatitis;
conditions of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable bowel syndrome, reflux oesophagitis, damage to the gastrointestinal tract resulting from infections by, for example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs;
and other conditions associated with inflammation.

The compounds will also be useful in the treatment and alleviation of acute pain or persistent inflammatory pain or neuropathic pain or pain of a central origin.

We are particularly interested in the conditions inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease and pain.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers and racemates may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above. For example, the compounds may be useful in the treatment of atherosclerosis, cystic fibrosis, hypotension associated with septic and/or toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-term immunosuppression in organ transplant therapy, in the control of onset of diabetes, in the maintenance of pancreatic function in diabetes, in the treatment of vascular complications associated with diabetes and in co-therapy with cytokines, for example TNF or interleukins.

The compounds of formula (I) may also be useful in the treatment of hypoxia, for example in cases of cardiac arrest and stroke, neurodegenerative disorders including nerve degeneration and/or nerve necrosis in disorders such as ischaemia, hypoxia, hypoglycaemia, epilepsy, and in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia, for example pre-senile dementia, Alzheimer's disease and AIDS-related dementia, Sydenham's chorea, Parkinson's disease, Tourette's syndrome, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, muscular dystrophy, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, pain, autism, seasonal affective disorder, jet-lag, depression or other symptoms associated with premenstrual syndrome (PMS), anxiety and septic shock. Compounds of formula (I) may also be expected to show activity in the prevention and reversal of drug addiction or tolerance such as tolerance to opiates and diazepines, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders, cancer and in the induction of labour.

We are particularly interested in the conditions stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia, migraine, cancer, septic shock and pain.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the

disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, inhalation, intravenous, topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

According to the invention, we further provide a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX inhibitor, more particularly in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib

and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The invention is illustrated, but in no way limited, by the following examples:

The following abbreviations are used:- DMSO (dimethylsulfoxide), DMF (*N,N*-dimethylformamide), THF (tetrahydrofuran), NMP (*N*-methylpyrrolidinone).

Example 1

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-hydroxy-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate and 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-hydroxy-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

To a stirred solution of 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate (6.9 g) in dry THF (100 ml) at 0 °C and under nitrogen, was added phenyl magnesium bromide (34 ml, 1M in THF). During the addition an exotherm to 20 °C occurred, and the mixture was kept at this temperature for 3 h. The reaction mixture was quenched with 5% aqueous citric acid (100 ml) and the products extracted into ethyl acetate (150 ml). The organic extract was dried ($MgSO_4$) and concentrated to an oil. The crude mixture of diastereomers was purified by chromatography (silica, 10% diethyl ether/*iso*hexane as eluent) to give the (4*S*, 2*S*) sub-title compound (3.5 g, 38%) as a colourless solid .

^{1}H NMR 400MHz ($CDCl_3$) 7.4-7.2 (5H, m), 4.88 (1H, d), 4.65 (1H, m), 4.35 (1H, m), 4.0 (1H, m), 3.65 (1H, d), 2.1-2 (1H, m), 1.85-1.95 (1H, m), 1.6 (3H, s), 1.49 (12H, s).

Further elution gave the (4*S*, 2*R*) sub-title compound (2.5 g, 27%) as a colourless solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.4-7.3 (5H, brs), 4.77-4.73 (1H, m), 4.3-3.7 (3H, m), 2.2-2 (2H, m), 1.6-1.4 (15H, m).

b) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-(benzoylthio)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

To a solution of the (4*S*, 2*S*) product from step (a) (3 g) and tris(4-chlorophenyl)phosphine in dry THF at 0 °C was added diisopropylazodicarboxylate (1.84 ml) dropwise over 5 minutes. After the addition was complete the mixture was stirred for 20 minutes and then thiobenzoic acid (1.1 ml) added. The cooling bath was removed and stirring continued overnight. The mixture was concentrated and the residue was purified by chromatography (silica, 10% diethyl ether/*iso*hexane as eluent) to give the sub-title compound (1.2 g, 29%) as a yellow coloured solid.

MS APCI +ve $^m/z$ 342 ([M+H-Boc]$^+$).

c) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-[(3-cyano-6-methyl-2-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

A mixture of the product from step (b) (440 mg), 2-chloro-6-methyl-3-pyridinecarbonitrile (229 mg), sodium carbonate (159 mg) and water (1 ml) in methanol (10 ml) was stirred at room temperature for 17 h. The mixture was diluted with water (50ml) and extracted with diethyl ether (2 x 50 ml). The combined extracts were dried ($MgSO_4$) and concentrated to an oil and purified by chromatography (silica, 10% diethyl ether/*iso*hexane as eluent) to afford the protected amino alcohol.

MS APCI +ve $^m/z$ 454 [M+H]$^+$.

d) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

The total product from step (c) was dissolved in ethylene glycol (2 ml), a crystal of pyridinium tosylate added and the solution heated at 190 °C for 10 minutes. The mixture was cooled to ambient temperature, diluted with methanol (50 ml), and the solution stirred with SCX resin. The resin was collected by filtration and treated with methanolic ammonia. The ammonia solution was concentrated to dryness and the residue purified by chromatography (silica, 10% 7M methanolic ammonia in dichloromethane as eluent) to afford the free base (70 mg, 22%). The amine was converted into the ethanedioate salt using one equivalent of oxalic acid in ethanol to afford the title compound.

MS APCI +ve $^{m}/z$ 314 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.1-7.2 (7H, m), 5.33 (1H, t), 3.6-3.4 (2H, m), 2.93 (1H, br m), 2.59 (3H, s), 2.35-2.2 (2H, m).

Example 2

2-[[(3S)-3-Amino-4-hydroxy-1-(3-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

a) (4S)-4-[2-(3-Isoxazolyl)-2-oxoethyl]-2-oxazolidinone

Dibromoethane (0.4 g) was added to a suspension of zinc dust (1.3 g) in dry THF (4 ml) under nitrogen, and the mixture heated to ca. 60 °C. After immediately cooling to room temperature, further dibromoethane (0.4 g) was added and the heat / cool cycle was repeated. THF (5 ml) and chlorotrimethylsilane (0.2 ml) were added and the mixture stirred for 2 minutes. A solution of (4*R*)-4-(iodomethyl)-2-oxazolidinone (2.26 g) in THF (4 ml) was added dropwise (a slight exotherm was observed) and the reaction heated at 30 °C for 1 h. After cooling to room temperature, THF (6 ml) was added and the suspension was left to stand for 1 h. The supernatant was transferred by cannula over 5 minutes into a solution of lithium chloride (0.84 g) and copper (I) cyanide (0.88 g) in THF (8 ml) at –78 °C under nitrogen (the salts had previously been stirred together for 10 minutes at room temperature). The mixture was warmed to 0 °C, re-cooled to –78 °C and a solution of 3-

isoxazolecarbonyl chloride (0.78 g) in THF (1 ml) added. After 1 h, the mixture was warmed to –10 °C and left to slowly warm to room temperature over 16 h. The reaction mixture was poured into a mixture of ethyl acetate and saturated ammonium chloride solution and the mixture filtered through celite. The organic layer was then separated and washed with water and brine and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography (silica, 25 to 100% ethyl acetate/*iso*hexane as eluent) to give the sub-title compound (0.82 g, 70%) as an oily solid.

^{1}H NMR 400MHz (d_6-DMSO) 9.15 (1H, s), 7.71 (1H, s), 6.95 (1H, s), 4.50 (1H, t), 4.26 (1H, quintet), 4.03 (1H, dd), 3.44 (1H, dd), 3:30 (1H, m).

b) (4*S*)-4-[2-Hydroxy-2-(3-isoxazolyl)ethyl]-2-oxazolidinone

Borane (4.16 ml of a 1M solution in THF) was added to a solution of (*R*)-2-methyl-CBS-oxazaborolidine (0.42 ml, 1M solution in toluene) in THF (4 ml) at 0 °C. After 10 minutes, a solution of (4*S*)-4-[2-(3-isoxazolyl)-2-oxoethyl]-2-oxazolidinone (0.82 g) in THF (3 ml) was added over 5 minutes and the resultant solution was stirred at 0 °C for 1h and at 20 °C for 18h. Methanol (25 ml) was added and the mixture was stirred for 15 minutes. The mixture was evaporated, re-dissolved in methanol and re-concentrated *in vacuo* 2 more times. The residue was purified by chromatography (silica, ethyl acetate as eluent) to give the sub-title compound (0.55 g) as a colourless oil; 1.5:1 mixture of diastereomers by NMR.

^{1}H NMR 400MHz (d_6-DMSO) (major diastereomer) 8.27 (1H, s), 7.83 (1H, s), 6.56 (1H, s), 5.70 (1 H, d), 4.83 (1H, m), 4.45-4.37 (1H, m), 4.00 (2H, m), 2.01-1.82 (2H, m).

c) (4S)-4-[2-(Benzoylthio)-2-(3-isoxazolyl)ethyl]-2-oxazolidinone

To a solution of triphenylphosphine (1.45 g) in THF (30 ml) at 0 °C under nitrogen was added diisopropylazodicarboxylate (1.15 ml) dropwise. After 45 minutes, a solution of thiobenzoic acid (0.77 g) and the product from step (a) (0.547 g) in THF (10 ml) was added dropwise. The reaction was warmed to room temperature and stirred for 16 h. The solvent was evaporated, and the residue purified by chromatography (silica, 2 to 75% ethyl

acetate/*iso*hexane as eluent) to give the sub-title compound (1.2 g) (1.5:1 diastereomeric mixture) as an oily solid.

^{1}H NMR 400MHz (d_6-DMSO) 8.91 (1H, s), 8.02-7.53 (6H, m), 6.71 (1H, s), 5.08 (1H, dd), 4.33 (1H, t), 4.01 (1H, dd), 3.76 (1H, quintet), 2.34 (1H, m), 2.17 (1H, m).

d) 2-[[1-(3-Isoxazolyl)-2-[(4*S*)-2-oxooxazolidinyl]ethyl]thio]-6-methyl-3-pyridinecarbonitrile

The product from step (c) (0.6 g) was dissolved in 7M ammonia in methanol (8 ml), stirred at room temperature under nitrogen for 2 h and then the solvent was evaporated. The residue was dissolved in DMF (5 ml) and a mixture of caesium carbonate (0.85 g) and 2-chloro-6-methyl-3-pyridinecarbonitrile (0.2 g) added. After stirring for 3 h, ethyl acetate and water were added, and the organic layer separated. The aqueous layer was further extracted with ethyl acetate. The combined organic extracts were washed with 1M aqueous sodium hydroxide solution and brine, then dried (Na_2SO_4). The solvent was evaporated and the residue purified by chromatography (silica, 40 to 80% ethyl acetate/*iso*hexane as eluent) to give the sub-title compound (0.15 g) (3:1 diastereomeric mixture) as an oily solid.

^{1}H NMR 400MHz (d_6-DMSO) 8.92 (1H, d), 8.13 (1H, d), 8.01 (1H, bs), 7.25 (1H, d), 6.74 (1H, d), 5.45 (1H, dd), 4.30 (1H, t), 4.00 (1H, dd), 3.74 (1H, m), 2.58 (3H, s), 2.40-2.20 (2H, m).

e) 1,1-Dimethylethyl (4*S*)-4-[2-[(3-cyano-6-methyl-2-pyridinyl)thio]-2-(3-isoxazolyl)ethyl]-2-oxo-3-oxazolidinecarboxylate

To a solution of the product from step (d) (0.15 g) in THF (2 ml) were added sequentially triethylamine (0.10 ml), carbonic acid, (1,1-dimethylethoxy)carbonyl 1,1-dimethylethyl ester (0.15 g) and dimethylaminopyridine (13 mg), and the solution was then stirred for 16 h. Diethyl ether and water were added and the organic layer separated. The organic extract was washed with aqueous potassium hydrogensulfate solution and brine, then dried over (Na_2SO_4). The solvent was evaporated and the residue purified by chromatography (silica,

40 to 50% ethyl acetate in isohexane as eluent) to give the sub-title compound (70 mg) as a white solid.

^{1}H NMR 400MHz (d_6-DMSO) (major diastereomer) 8.91 (1H, d), 8.15 (1H, d), 7.27 (1H, d), 6.74 (1H, d), 5.47 (1H, dd), 4.50-4.30 (3H, m), 2.57 (3H, s), 2.60-2.40 (2H, m), 1.44 (9H, s).

<u>f) 1,1-Dimethylethyl [(1*S*)-3-[(3-cyano-6-methyl-2-pyridinyl)thio]-1-(hydroxymethyl)-3-(3-isoxazolyl)propyl]carbamate</u>

To a solution of the product from step (e) (70 mg) in methanol (2.4 ml) was added caesium carbonate (0.01 g) and the solution stirred for 3 h. Ethyl acetate and water were added, and the organic layer was separated. The organic extract was washed with brine, dried (Na_2SO_4), evaporated and the residue purified by chromatography (silica, 50 to 60% ethyl acetate/*iso*hexane as eluent) to give the sub-title compound (54 mg) as a white solid.

^{1}H NMR 400MHz ($CDCl_3$) (major diastereomer) 8.38 (1H, d), 7.72 (1H, d), 7.00 (1H, d), 6.43 (1H, d), 5.42 (1H, d), 5.22 (1H, s), 3.80-3.67 (2H, m), 3.61 (1H, dt), 2.66 (3H, s), 2.54 (2H, m), 2.20 (1H, m), 1.45 (9H, s).

<u>g) 2-[[(3S)-3-Amino-4-hydroxy-1-(3-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate</u>

The product from step (f) (60 mg) was dissolved in 4M HCl in dioxane (5 ml). After 2 h, the volatiles were removed, the residue taken up in methanol and passed through a SCX ion exchange resin eluting with methanol followed by 7M ammonia in methanol. The solvents were removed to afford the free base of the title product (50 mg). This material was taken up in acetonitrile (3 ml) and methanol (1 ml) and a solution of oxalic acid (14 mg) in diethyl ether added. The solvents were removed, ethyl acetate added, and the crystals filtered off and dried to give the title compound (30 mg) as a cream solid as an 80:20 (1*R*):(1*S*) diastereomeric mixture.

MS APCI +ve $^m/z$ 305 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.92 (1H, d), 8.16 (1H, d), 7.99 (ca. 2H, vbs), 7.29 (1H, d), 6.68 (1H, d), 5.55 (1H, t), 3.63 (1H, dd), 3.52 (1H, dd), 3.20 (1H, bs), 2.58 (3H, s), 2.40-2.20 (2H, m).

Example 3

4-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(5-cyano-2-methyl-4-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The product from Example 1 step (b) (406 mg) was treated with 7M ammonia in methanol (30 ml) and stirred at room temperature for 6h.The solvent was evaporated, the residue dissolved in dry DMF (25 ml) and treated with 4-chloro-6-methyl-3-pyridinecarbonitrile (154 mg) followed by caesium carbonate (600 mg) under nitrogen. The reaction mixture was stirred for 24 h, poured into brine and ethyl acetate and the organic layer separated, washed with water (5 times) and then brine and dried ($MgSO_4$).The solvent was evaporated and the residue purified by chromatography (silica, 5% ethyl acetate/dichloromethane as eluent) to give the sub-title compound (177 mg, 42%) as a viscous oil.

MS APCI +ve $^m/z$ 454 $[M+H]^+$.

b) 4-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

The product from Example 3 step (a) (177 mg) was stirred in 4M HCl in dioxane (5 ml) and methanol (5 ml) for 1h. The reaction mixture was evaporated, azeotroped with ether (3 times), then treated with 1 equivalent of oxalic acid in ethanol (10 ml). The clear solution was treated with ether until complete precipitation and the solid collected by filtration, washed with ether and dried *in vacuo* at 40 °C for 2 h to give the title compound (76 mg, 48%) as a light brown solid.

MS APCI + ve $^m/z$ 314 $[M+H]^+$.

^1H NMR 300MHz (d_6-DMSO) 8.7 (1H, s), 7.54 (3H, m), 7.40 (2H, m), 7.31 (1H, m), 5.15 (1H, t), 3.48 (1H, dd), 3.38 (1H, m), 2.90 (1H, br m), 2.50 (3H, s), 2.30 (1H, m), 2.14 (1H, m).

Example 4

3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[[2-cyano-5-(trifluoromethyl)-3-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The product from Example 1 step (b) (411 mg) was stirred in 7M ammonia in methanol (30 ml) for 6 h. The solvent was evaporated, the residue dissolved in dry DMF (25 ml) and treated under nitrogen with stirring with 3-chloro-5-(trifluoromethyl)-2-pyridinecarbonitrile (210 mg) followed by caesium carbonate (610 mg). The reaction mixture was stirred under nitrogen overnight at room temperature, poured into brine and ethyl acetate, and the organic layer separated, washed with water (5 times) then brine and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography (silica, 5% ethyl acetate/*iso*hexane as eluent) to give the sub-title compound (190 mg, 40%) as a viscous oil.

MS APCI +ve $^m/z$ 408 $[M\text{-}Boc+1]^+$.

b) 3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile ethanedioate

The product from Example 4 step a) (190 mg) was stirred in 4 M hydrogen chloride in dioxane (5 ml) and methanol (5 ml) for 1 h. The reaction mixture was evaporated, the residue treated with aqueous sodium bicarbonate and ethyl acetate, and the organic layer separated and dried ($MgSO_4$). The solvent was evaporated and the residue treated with an equivalent of oxalic acid in ethanol. The solution was evaporated and the residue treated with acetonitrile and a few drops of ether to precipitate a colourless solid which was

collected by filtration, washed with ether and dried to give the title compound (133 mg, 78%).

MS APCI +ve $^m/z$ 368 $[M+H]^+$.

^{1}H NMR 300MHz (d_6-DMSO) 8.98 (1H, s), 8.33 (1H, s), 7.34 (5H, m), 5.04 (1H, t), 3.58 (1H, dd), 3.48 (1H, m), 3.05 (1H, m), 2.33 (1H, m), 2.18 (1H, m).

Example 5

2-[[(*1R,3S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethyl)-3-pyridinecarbonitrile (*E*)-butenedioate

a) 6-(Difluoromethyl)-2-(methylthio)-3-pyridinecarbonitrile

To a solution of 6-formyl-2-(methylthio)-3-pyridinecarbonitrile (1 g) in dichloromethane under nitrogen was added [bis(methoxyethyl)amino]sulfur trifluoride (2 ml) followed by ethanol (0.05 ml). After 16 h, the reaction mixture was cautiously poured into saturated aqueous sodium bicarbonate solution. The organic layer was separated and the aqueous layer extracted with further dichloromethane. The combined organic layers were dried ((sodium sulphate)) and the solvent removed. The residue was taken up in methanol and passed through a SCX ion exchange resin eluting with methanol. The solvents were removed to afford the title product (1.2 g) as a yellow solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.93 (1H, d), 7.38 (1H, d), 6.59 (1H, t), 2.65 (3H, s).

b) 6-(Difluoromethyl)-2-(methylsulfonyl)-3-pyridinecarbonitrile

To a solution of the product from Example 5 step (a) (1.2 g) in dichloromethane (12 ml) at 0 °C was added 3-chloroperoxybenzoic acid (6.8 g of minimum 57% purity). The reaction was warmed to room temperature and stirred for 2 h. The reaction was washed with aqueous sodium bicarbonate solution and dried over (Na_2SO_4). The solvent was evaporated and the residue taken up in diethyl ether. The organic solution was washed with aqueous sodium metabisulfite solution, ice cold aqueous 0.5M sodium hydroxide solution, brine,

and then dried (Na_2SO_4). The solvent was removed to give the sub-title compound (0.58 g) as a pale yellow oil.

^{1}H NMR 400MHz ($CDCl_3$) 8.44 (1H, d), 8.03 (1H, d), 6.72 (1H, t), 3.42 (3H, s).

c) 1,1-Dimethylethyl (4*S*)-4-[[(2*R*)-2-[[3-cyano-6-(difluoromethyl)-2-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The title compound was prepared by the method of Example 4 step (a) using the product of Example 1 step (b) and 6-(difluoromethyl)-2-(methylsulphonyl)-3-pyridinecarbonitrile to give, after purification by chromatography (silica, 5% ethyl acetate in isohexane as eluent) the sub-title compound (252mg, 74%) as a viscous oil.

MS APCI +ve m/z 390 $[M\text{-}Boc +1]^+$.

d) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethyl)-3-pyridinecarbonitrile (*E*)-butenedioate

The product from step (c) was deprotected as in Example 4 step (b) and then converted into the (*E*)-butenedioate salt by addition of one equivalent of fumaric acid to give the title compound (121 mg, 51%) as a colourless foam.

MS APCI +ve $^m/z$ 350 $[M+H]^+$.

^{1}H NMR 300MHz (d_6-DMSO) 8.40 (1H, d), 7.59 (1H, d), 7.52 (2H, d), 7.31 (3H, m), 7.10 (1H, t), 6.45 (2H, s), 5.35 (1H, q), 3.38 (2H, m), 2.75 (1H, br m), 2.31 (1H, m), 2.18 (1H, m).

Example 6

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(fluoromethyl)-3-pyridinecarbonitrile (*E*)-butenedioate

a) 6-(Fluoromethyl)-2-(methylthio)-3-pyridinecarbonitrile

To a solution of 6-formyl-2-(methylthio)-3-pyridinecarbonitrile (1 g) in ethanol (12 ml) was added sodium borohydride (0.212 g). After 2 h, the volatiles were removed and ethyl acetate and water added. The organic layer was separated and the aqueous layer extracted with further ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent removed to afford 6-(hydroxymethyl)-2-(methylthio)-3-pyridinecarbonitrile (1 g) as yellow solid. This material was taken up in dichloromethane (10 ml) under nitrogen and [bis(methoxyethyl)amino]sulfur trifluoride (1 ml) in dichloromethane (3 ml) was added. After 16 h the reaction mixture was cautiously poured into saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried (Na_2SO_4) and the solvent removed. The residue was taken up in methanol and passed through a SCX ion exchange resin eluting with methanol. The solvents were removed to afford the sub-title product (0.88 g) as a yellow solid.

^{1}H NMR 400MHz ($CDCl_3$) 7.85 (1H, d), 7.23 (1H, d), 5.48 (2H, d), 2.60 (3H, s).

b) 6-(Fluoromethyl)-2-(methylsulfonyl)-3-pyridinecarbonitrile

The title compound was prepared by the method of Example 5 step (b) using the product of Example 6 step (a) and 3-chloroperoxybenzoic acid. The product was obtained as a pale green oil which solidified upon standing.

^{1}H NMR 400MHz ($CDCl_3$) 8.33 (1H, d), 7.87 (1H, d), 5.60 (2H, d), 3.37 (3H, s).

c) 1,1-Dimethylethyl (4*S*)-4-[[(2*R*)-2-[[3-cyano-6-(fluoromethyl)-2-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The title compound was prepared by the method of Example 4 step (a) using the product of Example 1 step (b) and 6-(fluoromethyl)-2-(methylsulphonyl)-3-pyridinecarbonitrile to give, after chromatography (silica, 10 to 30% diethyl ether in isohexane as eluent) the sub-title compound (318 mg) as an off white foam.

^{1}H NMR 400MHz (d_6-DMSO) 8.26 (1H, d), 7.46 (2H, d), 7.35 (3H, m), 7.25 (1H, t), 5.76-5.44 (2H, m), 5.14 (1H, dd), 4.00-3.53 (3H, br m), 2.50-2.00 (2H, m), 1.46-1.36 (15H, m).

d) 2-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(fluoromethyl)-3-pyridinecarbonitrile (*E*)-butenedioate

The product from step (c) was deprotected as in Example 4 step (b) and then converted into the (*E*)-butenedioate salt by addition of one equivalent of fumaric acid to give the title compound (224 mg) as an off white foam.

MS APCI +ve $^{m}/z$ 332 $[M+H]^+$.

^{1}H NMR 400MHz (CD_3OD) 8.07 (1H, d), 7.49 (2H, m), 7.38-7.27 (4H, m), 6.68 (2H, s), 5.62 (1H, q), 5.49 (1H, t), 3.69 (1H, dd), 3.55 (1H, dd), 3.26 (1H, m), 2.43 (1H, ddd), 2.34 (1H, ddd).

Example 7

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridinyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile Dihydrochloride

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]-2,2-dimethyl- 3-oxazolidinecarboxylate

The title compound was prepared by the method of Example 1 step (a) to give the more polar diastereomer as a colourless oil.

MS APCI +ve $^{m}/z$ 222 $[M+H\text{-}Boc]^+$.

b) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-(5-chloro-2-cyano-4-fluorophenoxy)-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

Sodium hydride (60% in mineral oil) (24 mg) was added cautiously to a stirred solution of 4-chloro-2,5-difluorobenzonitrile (90 mg) and the product from step (a) (165 mg) in dry DMF (5 ml) and stirring was continued for 2 h. The reaction mixture was quenched with water, extracted twice with ethyl acetate, the extracts dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (silica, 10% ethyl acetate/hexanes as eluent) to give the sub-title compound (220 mg) as a colourless foam.

MS APCI +ve $^{m}/z$ 376 $[M+H\text{-}Boc]^+$.

c) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridinyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile dihydrochloride

The product from step (b) (220 mg) was stirred with methanol (1 ml) and 4 M hydrogen chloride in dioxane (2 ml) for 2 h. The reaction mixture was evaporated and triturated with diethyl ether to give the title compound (130 mg) as a white solid.

MS APCI +ve $^{m}/z$ 336 $[M+H]^+$.
^{1}H NMR 400MHz (d_6-DMSO) 8.95 (1H, s), 8.75 (1H, d), 8.27-8.21 (4H, m), 8.06 (1H, d), 7.81-7.78 (1H, t), 7.62 (1H, d), 6.23-6.20 (1H, m), 3.72-3.65 (1H, dd), 3.61-3.58 (1H, m), 3.3-3.2 (1H, br.s), 2.40-2.31 (1H, m), 2.27-2.20 (1H, m).

Example 8

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-hydroxy-2-(2-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate and 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-hydroxy-2-(2-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

To a stirred solution of (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylic acid 1,1-dimethylethyl ester (10.75 g) in dry dichloromethane (225 ml) at room temperature and under nitrogen, was added 2-(trimethylsilyl)thiazole (10.6 ml). The mixture was then stirred at room temperature for 18 h. The reaction mixture was evaporated to dryness and the residues dissolved in THF (27 ml) and tetrabutylammonium fluoride (1.0M in THF, 6 ml) added. The mixture was then stirred at room temperature for 2 h. The resultant mixture was evaporated to dryness, water (80 ml) added, and the mixture was extracted with dichloromethane four times. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to an oil. The crude mixture of diastereomers was purified by

chromatography (silica, 20 to 60% ethyl acetate/*iso*hexane as eluent) to give the (4*S*, 2*S*) isomer (7.6 g) as a pale yellow oil.

MS APCI +ve $^{m}/z$ 329 $[M+H]^{+}$.
^{1}H NMR 400MHz ($CDCl_3$) 7.71 (1H, d), 7.28 (1H, d), 5.14 (1H, m), 5.07 (1H, m), 4.20 (1H, m), 4.05 (1H, m), 3.85 (1H, m), 2.20-2.50 (2H, m), 1.48 (15H, m).

Further elution gave the (4*S*, 2*R*) isomer (6.4 g) as a colourless solid.

MS APCI +ve $^{m}/z$ 329 $[M+H]^{+}$.
^{1}H NMR 400MHz ($CDCl_3$) 7.72 (1H, d), 7.28 (1H, d), 5.68 (1H, d), 4.94 (1H, m), 4.35 (1H, m), 4.04 (1H, m), 3.71 (1H, d), 2.42 (1H, m), 1.90 (1H, m), 1.62 (3H, s), 1.53 (3H, s), 1.51 (9H, s).

<u>b) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-(5-chloro-2-cyano-4-fluorophenoxy)-2-(2-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate</u>
To a solution of the (4*S*, 2*R*) isomer from step(a) (3 g) and 4-chloro-2,5-difluorobenzonitrile (1.59 g) in dry THF (100 ml) containing dry DMF (10 ml) at room temperature was added sodium hydride (60% in oil, 385 mg). After the addition was complete the mixture was stirred for 18 h and then poured into water (60 ml) and extracted with diethyl ether (3 times). The combined organic extracts were washed with brine and dried ($MgSO_4$). The mixture was evaporated to dryness to give an oil which was purified on silica gel eluting with 20 to 25% ethyl acetate in isohexane. The title compound was isolated as a yellow coloured oil (4.0 g, 91%).

MS APCI +ve $^{m}/z$ 482/4 $[M+H]^{+}$.

<u>c) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile ethanedioate</u>

To a solution of the product from step (b) (4.0 g) in methanol (100 ml) was added a solution of 4M HCl in dioxane. The mixture was stirred at 20 °C for 1.5 h, then evaporated

to dryness. The residue was dissolved in aqueous sodium bicarbonate solution and extracted with ethyl acetate (four times). The combined extracts were washed with brine, dried ($MgSO_4$) and purified by chromatography (silica, ethyl acetate, then 10% (7M ammonia in methanol) in dichloromethane as eluents) to give a mixture which was concentrated and dissolved in a mixture of ethanol and acetonitrile. A solution of oxalic acid (730 mg) in diethyl ether was added and the resultant mixture was evaporated to dryness then recrystallised from a mixture of ethanol, acetonitrile and diethyl ether to give the title compound (2.14 g) as a white solid.

MS APCI +ve $^{m}/z$ 342/4 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.07 (1H, d), 7.89 (1H, d), 7.84 (1H, d), 7.70 (1H, d), 6.24 (1H, m), 3.67 (1H, m), 3.55 (1H, m), 3.29 (1H, m), 2.30-2.44 (2H, m).

Example 9

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(5-isothiazolyl)butyl]oxy]-4-chloro-5-fluoro benzonitrile Hydrochloride

a) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-hydroxy-2-(5-isothiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate and 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-hydroxy-2-(5-isothiazolyl)ethyl]- 2,2-dimethyl-3-oxazolidinecarboxylate

A solution of isothiazole (1.42 g) in dry THF (50 ml) under a nitrogen atmosphere was cooled to –78 °C and butyl lithium (1.6M in hexanes, 10.3 ml) added dropwise keeping the temperature below -70 °C. The resulting red solution was stirred at –78 °C for 1 h, then a solution of 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate (4 g) in dry THF (20 ml) was added over 5 minutes. After the addition was complete the cooling was removed and the mixture stirred for 30 minutes. The reaction mixture was poured into water (150 ml) and the products extracted into diethyl ether (2 x 150 ml). The combined extracts were dried ($MgSO_4$) and concentrated to an oil. Purification by chromatography (silica, 50% isohexane in diethyl ether as eluent) gave the (4*S*, 2*S*) sub-title compound (600 mg) as a colourless oil.

MS APCI +ve $^{m}/z$ 329 $[M+H]^+$.

Further elution gave the (4*S*, 2*R*) sub-title compound (500 mg) as a colourless oil.

MS APCI +ve $^{m}/z$ 329 $[M+H]^+$.

b) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(5-isothiazolyl)butyl]oxy]-4-chloro-5-fluoro benzonitrile Hydrochloride

A solution of the (4*S*, 2*R*) isomer from step (a) (500 mg) in a mixture of dry THF (20 ml) and dry DMF (2 ml) was treated with 4-chloro-2,5-difluorobenzonitrile (416 mg). To this mixture under nitrogen was added sodium hydride (60% dispersion in mineral oil, 91 mg). The mixture was then stirred for 3h at 20 °C. The reaction mixture was poured into water (100 ml), and the products extracted into diethyl ether (2 x 100 ml). The combined extracts were dried over ($MgSO_4$) and concentrated to an oil. The major product was isolated by column chromatography on silica gel (25% diethyl ether/ *iso*hexane as eluent) and dissolved in methanol (5 ml). The solution was treated with 4M HCl in dioxane (2 ml) and stirred for 2 h. Concentration of the solution to dryness and trituation with acetonitrile afforded the title compound (190 mg) as a colourless solid.

MS APCI +ve $^{m}/z$ 342 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.57 (1H,s), 8.07 (1H, d), 8.1 (3H, br s), 7.67 (1H, d), 7.54 (1H, s), 6.5 (1H, dd), 5.41 (1H, t), 3.7-3.5 (2H, m), 3.25 (1H, br m), 2.4-2.2 (2H, m).

Example 10

4-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile (*E*)-butenedioate

a) Phenylmethyl (3*S*)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-4-hydroxy-butanoate

A solution of 4-(phenylmethyl) *N*-[(1,1-dimethylethoxy)carbonyl]-1-(2,5-dioxo-1-pyrrolidinyl)) L-aspartate (75.0 g) in THF (200 ml) was added over 1 h to a suspension of sodium borohydride (6.84 g) in THF (60 ml) and water (90 ml) at –5 °C (internal temperature kept below 15 °C). Further sodium borohydride (6.8 g in two batches) was added and stirred for 45 min. The mixture was poured into cold, stirred, half-saturated ammonium chloride solution (600 ml) and extracted with ethyl acetate (twice). The organic layers were dried ($MgSO_4$) and evaporated to give the sub-title compound as a waxy solid (56.24 g).

MS APCI +ve $^{m}/z$ 210 $[M+H-BOC]^+$.
^{1}H NMR 300MHz ($CDCl_3$) 7.41-7.27 (5H, m), 5.24-5.10 (3H, m), 4.15-3.96 (1H, m), 3.71 (2H, d), 2.69 (2H, d), 1.44 (9H, s).

<u>b) Phenylmethyl (4*S*)-3-[(1,1-dimethylethoxy)carbonyl]-2,2-dimethyl-4-oxazolidine-acetate</u>

2-Methoxypropene (46 ml) was added over 20 min to a solution of the product from step a) (74.88 g) 2,2-dimethoxypropane (30 ml) and p-toluenesulfonic acid (1.21 g) in dichloromethane (300 ml) at 0 °C and stirred at 0 °C for 1 h and at 20 °C for 1 h. 1M $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3 x 200 ml). The organic layers were dried ($MgSO_4$) and evaporated to give a colourless oil which was dissolved in toluene (300 ml), 2,2-dimethoxypropane (45 ml) and p-toluenesulfonic acid (1.2 g) added and the mixture was heated at 80 °C for 2 h. On cooling, K_2CO_3 was added and the mixture was extracted with ethyl acetate (twice). The organic layers were dried ($MgSO_4$) and evaporated to give the sub-title compound (83.8 g) as a pale yellow oil.

^{1}H NMR 300MHz ($CDCl_3$) 7.36-7.28 (5H, m), 5.12 (2H, d), 4.38-3.97 (2H, m), 3.84 (1H, d), 3.05-2.48 (2H, m), 1.62-1.50 (6H, m), 1.46 (9H, s).

<u>c) (4*S*)-3-[(1,1-Dimethylethoxy)carbonyl]-2,2-dimethyl-4-oxazolidineacetic acid</u>

A suspension of palladium on carbon (10%, 3.8 g) and the product from step b) (83.8 g) in ethanol (250 ml) was stirred under hydrogen (4 atmospheres pressure) for 3.5h (5.3 l hydrogen uptake). The mixture was filtered through celite and evaporated. Ethyl acetate

(100ml) and 1M K_2CO_3 (200 ml) were added and the organic layer was separated and further extracted with 1M K_2CO_3 (40 ml) and 1M $NaHCO_3$ (40 ml). The aqueous layers were washed with ethyl acetate, combined and acidified at 0 °C by dropwise addition of 4M HCl (130ml). The aqueous was extracted with ethyl acetate (3 x 200 ml) and the organic layers were dried ($MgSO_4$) and evaporated to give the sub-title compound as a pale orange gum (56.24 g), which slowly crystallised.

^1H NMR 300MHz ($CDCl_3$) 4.33-4.12 (1H, m), 4.09-4.00 (1H, m), 3.86 (1H, d), 3.02-2.77 (1H, m), 2.62-2.50 (1H, m), 1.62-1.54 (6H, m), 1.53 (9H, s).

<u>d) 1,1-Dimethylethyl (4*S*)-4-[2-(methoxymethylamino)-2-oxoethyl]-2,2-dimethyl-3-oxazolidinecarboxylate</u>

N,O,-Dimethylhydroxylamine hydrochloride (21.4 g), EDCI (41.94 g), *N*-methylmorpholine (24 ml) and DMAP (26.4 g) were added to a solution of the product from step c) (59.2 g) in CH_2Cl_2 (400 ml) at 0 °C and then stirred at 20 °C for 18 h. 2M HCl (200 ml) was added, the organic layer was separated and the aqueous was further extracted twice. The organic layers were washed with 2M HCl (50 ml) and $NaHCO_3$ (2 x 100 ml), combined, dried ($MgSO_4$) and evaporated to give the sub-title compound (60.2 g).

MS APCI +ve $^m/z$ 303 $[M+H]^+$.

^1H NMR 300MHz ($CDCl_3$) 4.38-4.19 (1H, m), 4.08 (1H, dd), 3.87 (1H, t), 3.70 (3H, s), 3.17 (3H, s), 3.07-2.45 (2H, m), 1.63-1.42 (15H, m).

<u>e) 1,1-Dimethylethyl (4*S*) 2,2-dimethyl-4-(2-oxo-2-phenylethyl)-3-oxazolidinecarboxylate</u>

Phenyl magnesium bromide (231 ml, 1M in THF) was added over 15 min to a solution of the product from step d) (60.1 g) in THF (360 ml) at –10 to –5 °C and stirred for 2 h. Further phenyl magnesium bromide (7 ml, 3M in ether) was added and stirred at 0 °C for 1 h then quenched by the addition of saturated NH_4Cl (250 ml) and 2M HCl (150ml). The mixture was extracted with ethyl acetate (thrice) and the organic layers were washed with brine, combined, dried ($MgSO_4$) and evaporated to give the sub-title compound (64.8 g) as an off-white solid.

^{1}H NMR 300MHz ($CDCl_3$) 7.98 (2H, d), 7.64-7.40 (3H, m), 4.50-4.35 (1H, m), 4.15-4.05 (1H, m), 3.88-3.65 (2H, m), 3.49-3.36 and 3.25-3.01 (1H, m), 1.70-1.35 (15H, m).

f) 1,1-Dimethylethyl (4*S*) -4-[(2S)-2-hydroxy-2-phenylethyl]- 2,2-dimethyl 3-oxazolidinecarboxylate

Borane (176 ml, 1M in THF) was added to a solution of (*R*) methyl-CBS-oxazaborolidine (16 ml, 1M in toluene) in THF (20 ml) and cooled to –20 °C. A solution of the product from step e) (64.6 g) in THF (200 ml) was added over 1.5 h, keeping the internal temperature below –15 °C, and then stirring at this temperature for 22 h. Methanol (40 ml) was added slowly and the solution was evaporated and then azeotroped with methanol to give a pale yellow oil (69 g). Ether and 1M $KHSO_4$ (20 ml) were added and the mixture was filtered and evaporated. Purification by chromatography (silica, 40-60 petrol/ether as eluent) gave the sub-title compound (37.4 g) as a white solid, identical with the major product from Example 1 step a).

Further elution gave the (4*S*, 2*R*) isomer as a white solid (20.0 g) identical with the minor product from Example 1 step a).

g) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-(benzoylthio)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

Di*iso*propyl azodicarboxylate (21.5 ml) in THF (20 ml) was added dropwise to a solution of triphenylphosphine (28.73 g) in THF (230 ml) at –10 °C and the white suspension was stirred for 30 min. A solution of the product from step f) (17.58 g) and thiobenzoic acid (12.8 ml) in THF (100 ml) was added over 45 min at –10 °C and then stirred at –10 °C to 4 °C for 18 h. The solvent was removed *in vacuo*, ether added and stirred until a precipitate formed. The mixture was filtered and the solids washed with *iso*hexane/ether (1:1). The solution was washed with aqueous $NaHCO_3$ and the aqueous layer extracted with ether. The combined organic layers were dried ($MgSO_4$), evaporated and purified by chromatography (silica, 40-60 petrol/dichloromethane (1:1 then 0:1) as eluent) to give a solid. This was crystallised from *iso*hexane at –78 °C to give the sub-title compound (14.76 g) as a white solid, identical with the major product from Example 1 step b).

^{1}H NMR 300MHz ($CDCl_3$) 7.93 (2H, d), 7.61-7.21 (8H, m), 4.79 (1H, dt), 4.18-3.83 (3H, m), 2.64-2.35 (1H, m), 2.23-2.09 (1H, m), 1.62-1.41 (15H, m).

h) 2-Chloro-5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-pyridine

A suspension of 2-chloropyridine-4-carboxylic acid (100 g) in thionyl chloride (370 ml) was heated at 80°C for 4 h. The reaction mixture was evaporated *in vacuo*, the residue azeotroped with toluene and then taken up into dichloromethane (300 ml) The solution was added dropwise over 1 h at 0 °C to a solution of 2-amino-2-methylpropanol (118.8 g) in dichloromethane (300 ml) and then stirred at 20 °C for 16 h. Water (500 ml) was added and the mixture was extracted with dichloromethane (5x500 ml). A solid suspension, which formed during extraction, is the required intermediate amide and needs extensive extraction. The organic layer was dried ($MgSO_4$) and evaporated to leave the intermediate amide (125.5 g).

This was suspended in dichloromethane (200 ml) at 0 °C and thionyl chloride (100 ml) was added dropwise and stirred for 1 h. A thick precipitate formed and more dichloromethane (300 ml) is added and reaction stirred for a further hour. The solvent was removed *in vacuo* to give the product as the hydrochloride salt (120 g).

^{1}H NMR 300MHz (CD_3OD) 9.03 (1H, t), 8.42 (1H, dd), 7.80(1H, dd), 4.96 (2H, s), 1.68 (6H, s).

The solid was suspended in water (800 ml) and treated with solid $NaHCO_3$ (ca. 70 g portion-wise) until gas evolution ceased. The mixture was extracted with dichloromethane (2 x 500 ml), dried ($MgSO_4$) and evaporated to give the sub-title compound (99.5 g).

^{1}H NMR ($CDCl_3$) 8.90 (1H, dd), 8.17 (1H, dd), 7.37 (1H, dd), 4.14 (2H, s), 1.39 (6H, s).

i) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-2-methoxy-pyridine

The product from step h) (99.5 g) in methanol (500 ml) was treated with sodium methoxide (0.61 mol of a 25wt% solution in methanol) and heated at reflux for 12 hrs. The solvent was removed under reduced pressure and the residue taken up in water (200 ml) and

extracted with dichloromethane (2 x 300 ml). The extract was dried ($MgSO_4$) evaporated to dryness to give the sub-title compound as an orange oil (85 g).

^{1}H NMR 300MHz ($CDCl_3$) 8.68 (1H, dd), 8.10 (1H, dd), 6.75 (1H, dd), 4.09 (2H, s), 3.98 (3H, s), 1.37 (6H, s).

j) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-2-methoxy-4-(methylthio)-pyridine

To 2,2,6,6-tetramethylpiperidine (51.22 g) in THF, under nitrogen, at 0°C, was added n-BuLi (227 ml of 1.6M solution in hexanes) dropwise and stirred for 15 min. The reaction mixture was cooled to –78°C and the product from step i) (43.97 g) in THF (50 ml) was added dropwise. The cooling bath was removed and the reaction temperature was allowed to warm up to –20 °C and kept at this temperature for 30 min. It was then cooled to -78°C and dimethyldisulphide (80 ml) was dripped in. The reaction mixture temperature rose to –30°C during this addition. The cooling bath was then removed and the reaction was stirred to room temperature for 12 h. The resulting red solution was quenched with water and concentrated to ca. 600 ml on a rotary evaporator. Water was added (500 ml) and the mixture was extracted with ethyl acetate (2 x 600 ml). The combined organics were washed with citric acid (500ml of 1M aqueous solution), dried ($MgSO_4$) and evaporated to give the sub-title compound as a pale yellow solid, (58.5 g).

^{1}H NMR 300MHz ($CDCl_3$) 8.50 (1H, s), 6.52 (1H, s), 4.04 (2H, s), 3.97 (3H, s), 2.40 (3H, s), 1.40 (6H, s).

k) 6-Methoxy-4-(methylthio)-3-pyridinecarbonitrile

A stirred solution of the oxazoline from step j) (45 g) in pyridine (350ml) was treated with phosphorus oxychloride (68 ml) and the mixture stirred under reflux for 4.5 h. The dark brown solution was cooled to room temperature and cautiously poured onto ice (1 kg). The resulting suspension was filtered and the solid washed with water (300 ml), 2M HCl (100 ml) and again with water (300ml). The damp product was dissolved in dichloromethane (600ml) and the solution dried ($MgSO_4$). Activated charcoal was added (15g) and the suspension filtered. Concentration of the filtrate and trituration of the solid with 40-60 petrol gave the sub-title compound as a very pale pink solid (26 g).

^{1}H NMR 300MHz ($CDCl_3$) 8.31 (1H, s), 6.51 (1H, s), 3.98 (3H, s), 2.52 (3H, s).

l) 6-Methoxy-4-(methylsulfonyl)-3-pyridinecarbonitrile

A solution of the product from step k) (13 g) in dichloromethane (150 ml) was cooled to 0 °C and treated with portion-wise addition of MCPBA (21.74g of ~57% purity) over 10 min. The mixture was allowed to slowly warm up to 20 °C. After 8 hrs LC/MS indicated a mixture of sulphoxide / sulphone products (72:28). Additional MCPBA was added (7.2 g) and after a further 4 hrs LC/MS indicated a 50:50 mixture of products. More MCPBA was added (12 g) and stirring continued for a further 2 h before reaction was complete. The reaction was cooled to 0 °C and treated with excess aqueous sodium metabisulphite solution. The organic layer was washed with sat. $NaHCO_3$ (3 x 200 ml), dried ($MgSO_4$) and evaporated to give the sub-title compound as a white solid (11.2 g).

^{1}H NMR300MHz ($CDCl_3$) 8.69 (1H, s), 7.47 (1H,s), 4.09 (3H, s), 3.28 (3H, s).

m) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(5-cyano-2-methoxy-4-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

A solution of the product from step g) (10.0g) in methanol (75 ml) at 20 °C was treated with 7 *M* ammonia in methanol (50 ml) every hour for eight hours. The methanol was evaporated and the residue was dissolved in dry DMF (100 ml). The product from step l) (4.8 g) was added and allowed to dissolve, followed by caesium carbonate (7.38 g) and the mixture was stirred at 20 °C for 18 h. Ethyl acetate (200 ml) and water (200 ml) were added and the aqueous layer was separated and washed with ethyl acetate (2x 100 ml). The combined ethyl acetate layers were washed with water (3x 200 ml) and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a crude yellow gum. Purification by chromatography (silica, 30% ethyl acetate in *iso*hexane as eluent) gave the sub-title compound as a translucent foam (7.4 g).

MS APCI +ve $^m/z$ 470 ([M(+H)]$^+$).

^{1}H 300MHz ($CDCl_3$) 8.51 (1H, s), 7.56 (2H, d), 7.37 (2H, t), 7.27 (1H, t), 6.87-6.83 (1H, m), 4.98-4.84 (1H, m), 4.14-3.60 (3H, m), 3.85 (3H, s), 2.30-1.85 (2H, m), 1.49-1.38 (15H, s).

n) 4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile (*E*)-butenedioate

To a solution of the product from step m) (7.1 g) in methanol (100 ml) at 0 °C, was added 4*M* HCl in dioxane (100 ml). The mixture was stirred at 20 °C for 2 h and the solvent was removed *in vacuo*. The residue was partitioned between aqueous sodium bicarbonate (200 ml) and dichloromethane (200 ml). The aqueous phase was extracted with dichloromethane (2x 100 ml) and the combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound free base as a pale yellow oil (4.8 g).

MS (APCI+ve) $^m/z$ 330 $[M(+H)]^+$.
^{1}H 300MHz ($CDCl_3$) 8.27 (1H, s), 7.43 (2H, d), 7.34 (2H, t), 7.27 (1H, t), 6.65 (1H, s), 4.75 (1H, dd), 3.90 (3H, s), 3.51-3.27 (2H, m), 2.71-2.63 (1H, m), 2.12-1.88 (2H, m).

A solution of this compound in methanol (50 ml) was added to a solution of fumaric acid (1.6 g) in methanol (50 ml) and stirred at 20 °C. The solvent was removed *in vacuo* and the residue was triturated with acetonitrile. The precipitate was collected and washed with acetonitrile, and dried to give the title compound as a white solid (5.1 g), m.p. 172-173 °C.

MS (APCI+ve) $^m/z$ 330 $[M(+H)]^+$.
^{1}H 500MHz (DMSO-d_6) 8.53 (1H, s), 7.55 (2H, d), 7.39 (2H, t), 7.30 (1H, t), 7.00 (1H, s), 6.45 (2H, s), 5.15 (1H, dd), 3.89 (3H, s), 3.38 (2H, ddd), 2.73-2.65 (1H, m), 2.25-2.01 (2H, m).

Example 11

4-[[(1*R*,3*R*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile (*E*)-butenedioate.

a) 1,1-Dimethylethyl (4*R*)-4-(2-oxo-2-phenylethyl)-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared from 4-(phenylmethyl) *N*-[(1,1-dimethylethoxy)carbonyl]-*D*-aspartate, the enantiomer of the starting material in Example 10 step a), by the methods of Example 10 steps a) to e).

MS APCI +ve $^{m}/z$ 320 $[M+H]^+$.

^{1}H NMR 300MHz (d_6-DMSO) 7.98 (2H, d), 7.61-6.83 (3H, m), 4.69 (1H, bs), 4.10 (1H, t), 3.83-3.68 (2H ,bm), 3.15 (1H, m), 1.66-1.42 (15H, m)

b) 1,1-Dimethylethyl (4R)-4-[(2R)-2-(benzoylthio)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the methods of Example 10 steps f) and g) from the product from step a). The chiral reduction (step f) was carried out using (*R*) methyl-CBS-oxazaborolidine.

MS APCI +ve $^{m}/z$ 342 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 7.86 (2H, d), 7.85-7.24 (8H, m), 4.77 (1H, m), 4.01-3.87 (2H, m), 3.62 (1H,bs), 2.16 (2H, m), 1.47-1.36 (15H, m)

c) 4-[[(1*R*,3*R*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile, (*E*)-butenedioate.

The title product was prepared by the methods of Example 10 steps m) to n). M.p. 221-223 °C.

MS APCI +ve $^{m}/z$ 330 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) (90°C) 8.54 (1H, s), 7.54 (2H, d), 7.39 (2H, t), 7.30 (1H, t), 6.87 (1H, m), 6.45 (2H, m), 5.09 (1H, m), 3.88 (3H, s), 3.61-3.55 (2H, m), 2.88 (1H, m), 2.33-2.09 (2H, m)

Example 12

4-[[(1S,3R)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile, (*E*)-butenedioate

a) 1,1-Dimethylethyl (4R)-4-[(2S)-2-(benzoylthio)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate.

The sub-title compound was prepared by using (*S*) methyl-CBS-oxazaborolidine catalyst in the chiral reduction of the product from Example 11 step a) following the procedure of Example 10 steps f) to g).

MS APCI +ve $^{m}/z$ 342 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 7.85 (2H, d), 7.63 (1H, t), 7.50 (2H, t), 7.42 (2H, d), 7.34 (2H, t), 7.27 (1H, t), 4.80 (1H, m), 3.95 (1H, m), 3.85-3.13 (2H,m), 2.14 (2H, m), 1.45-1.36 (15H, m)

b) 4-[[(1S,3R)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile,(*E*)-butenedioate

The title compound was prepared by the methods of Example 10 steps m) to n) from the product of step a). M.p. 162.5-163 °C.

MS APCI +ve $^{m}/z$ 330 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.53 (1H, s), 7.55 (2H, d), 7.38 (2H, t), 7.30 (1H, t), 7.00 (1H, s), 6.44 (1H, s), 5.12 (1H, m), 3.89 (3H, s), 3.36-3.26 (2H, m), 2.62 (1H, m), 2.22-2.08 (1H, m), 2.01-1.95 (1H, m)

Example 13

4-[[(1S,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile (*E*)-butenedioate

a) 4-[(2S)-2-(Benzoylthio)-2-phenylethyl]-2,2-dimethyl-1,1-dimethylethyl (4S)-3-oxazolidinecarboxylate

The sub-title compound was prepared from the minor isomer of Example 1 step a), following the method of Example 10 step g).

MS APCI +ve $^m/z$ 342 $[M+H]^+$.

^{1}H NMR 300MHz (d_6-DMSO) 7.91 (2H, d), 7.57-7.23 (8H, m), 4.76 (1H, m), 4.17-3.61 (3H, m), 2.50-2.18 (2H,m), 1.66-1.41 (15H, m)

b) 4-[[(1*S*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile,(*E*)-butenedioate

The title compound was prepared by the methods of Example 10 steps m) to n) from the product of step a). M.p. 213-228°C.

MS APCI +ve $^m/z$ 330 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.53 (1H, s), 7.53 (2H, d), 7.39 (2H, t), 7.30 (1H, t), 7.96 (1H, s), 6.43 (2H, s), 5.08 (1H, t), 3.88 (3H, s), 3.58 (2H, m), 2.86 (1H, bs), 2.25-2.28 (1H, m), 2.08 (1H, m).

Example 14

4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethoxy)-3-pyridinecarbonitrile (*E*)-butenedioate

a) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3-(methylthio)-2-pyridinnol

To 2,2,6,6-tetramethylpiperidine (5.7 g) in THF, under nitrogen, at 0 °C, was added *n*-BuLi (16.4 ml of 2.5M solution in hexanes) dropwise and stirred for 15 min. The reaction mixture was cooled to –78 °C and 5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl) 2-pyridinol

(2.6 g) in THF (75 ml) was added dropwise. The cooling bath was removed and the reaction temperature was allowed to warm to –20 °C and kept at this temperature for 2 h. It was then cooled to –78 °C and dimethyldisulphide (4.9 ml) was added dropwise. There was an exotherm to –30 °C during this addition. The cooling bath was then removed and the reaction was stirred at 20 °C for 12 h. Water (50ml) was added and the resulting mixture was extracted with dichloromethane (2 x 60 ml). The combined organics were washed with citric acid (50ml of 1M aqueous solution), dried (Na_2SO_4) and evaporated to give the sub-title compound as a pale yellow solid, (3.75 g) which was a 50:50 mixture of starting reagent and product by NMR.

MS APCI +ve $^m/z$ 239 $[M+H]^+$.

^{1}H NMR 300MHz (d_6-DMSO): (product); 7.92 (1H, s), 6.28 (1H, s), 4.06 (3H, s), 2.50 (2H, s), 1.35 (6H, s)

<u>b) 2-(Difluoromethoxy)-5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-4-(methylthio)-pyridine</u>

The product from step a) (2.6 g) in NMP (5 ml) was treated with sodium hydride (1.7 g of a 60% dispersion in mineral oil) and heated at 50 °C for 3 h. Chlorodifluoromethane was then bubbled through the reaction mixture for 1 h. Water (50 ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 60 ml). The combined organics were washed with aqueous $NaHCO_3$, then brine, dried ($MgSO_4$) and evaporated to obtain an oil. The residue was purified by chromatography (silica, isohexane/ethyl acetate as eluent) to give sub-title compound (0.6 g) as an oil.

MS APCI +ve $^m/z$ 289 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.50 (1H, s), 7.50 (1H, t), 6.68 (1H, s), 4.06 (2H, s), 2.43 (3H, s), 1.56 (6H, s)

<u>c) 6-(Difluoromethoxy)-4-(methylthio)-3-pyridinecarbonitrile</u>

The sub-title compound was prepared by the method of Example 10 step k) using the product from step b).

^{1}H NMR 300MHz (d_6-DMSO) 8.30 (1H, s), 7.49 (1H, t), 6.68 (1H, s), 2.57 (3H, s)

d) 6-(Difluoromethoxy)-4-(methylsulfonyl)-3-pyridinecarbonitrile

The product from step c) (0.36 g) in acetone (15 ml) was treated with $NaHCO_3$ (1.1 g), then a solution of oxone (3 g) in water (15 ml) was added dropwise and stirred at room temperature for 5 h. Water was added and the resulting mixture was extracted with ethyl acetate (3 x 50 ml). The combined organics were washed with water, brine and dried ($MgSO_4$) and then evaporated to give the sub-title compound as a pale yellow solid, (0.25 g).

^{1}H NMR 300MHz (d_6-DMSO) 8.75 (1H, s), 7.67 (1H, s), 7.51 (1H, t), 3.38 (3H, s)

e) 4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethoxy)-3-pyridinecarbonitrile (*E*)-butenedioate

The title compound was prepared by the method of Example 10 steps m) to n) using product from step d). M.p. 144-146 °C.

MS APCI +ve $^m/z$ 366 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.61 (1H, s), 7.65 (1H, t), 7.65-7.37 (7H, m), 6.54 (2H, s), 5.34 (1H, m), 3.47 (2H, m), 2.88 (1H, bs), 2.27 (2H, m).

Example 15

2-[[(1*R*,3*R*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile Hydrochloride

a) 1,1-Dimethylethyl (4*R*) 4-[(2*R*)-2-[(3-Cyano-6-methyl-2-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The product from Example 11 step b), (190 mg) and 2-chloro-6-methyl-3-pyridinecarbonitrile (220 mg) were dissolved in 7M ammonia in methanol (5 ml) and stirred at ambient temperature for 18 hr. The reaction mixture was evaporated to dryness

and the residue was purified by chromatography (silica, dichloromethane as eluent) to give sub-title compound (110 mg) as a gum.

MS APCI +ve $^{m}/z$ 454 [M+H]$^{+}$.

b) 2-[[(1*R*,3*R*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile Hydrochloride

A solution of the product from step a) (110 mg) in 4M HCl in dioxane (2 ml) was stirred at 20 °C for 2 hr. The solvent was removed *in vacuo* and the residue triturated with acetonitrile to give the title compound as a white solid (42 mg).

MS APCI +ve $^{m}/z$ 314 [M+H]$^{+}$.

^{1}H NMR 300MHz (d_6-DMSO) 8.1 (1H, d), 7.54-7.28 (5H, m), 5.36 (1H, t), 5.22-5.17 (1H, m) 3.81-3.75 (1H, m), 3.62-3.54 (1H, m) 3.32 (3H, s), 2.8-2.7 (1H, m), 2.53-2.46 (1H, m).

Example 16

4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-($^{2}H_3$)methoxy-3-pyridinecarbonitrile (*E*)-2-butenedioate

a) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-2-($^{2}H_3$)methoxy-pyridine

Sodium hydride (800 mg) was added to a solution of the product from Example 10 step h) (2.1 g) and methyl-d_3-alcohol-d (720 mg) in DMF (50 ml). The reaction mixture was heated at 65 °C for 2 h and then allowed to cool to room temperature. The mixture was poured into water (1000 ml) and extracted with ethyl acetate (twice). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the sub-title compound (2.3 g) as a colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 8.68 (1H, s), 8.10 (1H, d), 6.72 (1H, d), 4.09 (2H, s), 1.37 (6H, s).

b) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-2-($^{2}H_3$)methoxy-4-(methylthio)-pyridine

The sub-title compound was prepared by the method of Example 10 step j) using the product from step a).

MS APCI +ve $^{m}/z$ 256 ($[M(+H)]^+$).

c) 6-($^{2}H_3$)Methoxy-4-(methylthio)-3-pyridinecarbonitrile

The sub-title compound was prepared by the method of Example 10 step k) using the product from step b).

MS APCI +ve $^{m}/z$ 184 ($[M(+H)]^+$).

d) 6-($^{2}H_3$)Methoxy-4-(methylsulfonyl)- 3-pyridinecarbonitrile

A solution of Oxone (11.1 g) in water (40 ml) was added to a suspension of the product from step c) (1.1 g) in acetone (40 ml) and sodium bicarbonate (4.16 g). The reaction mixture was then stirred at room temperature for 24 h. Water and ethyl acetate were then added until a complete solution was achieved. The organic phase was separated and dried ($MgSO_4$), filtered and concentrated to give the sub-title compound (1.3 g) as a colourless solid.

MS APCI +ve $^{m}/z$ 216 ($[M(+H)]^+$).

e) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(2-($^{2}H_3$)methoxy -5-methyl-4-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product from step d).

MS APCI +ve $^{m}/z$ 373 ($[M(+H)-BOC]^+$).

f) 4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-($^2H_3$)methoxy-3-pyridinecarbonitrile (*E*)-2-butenedioate

The title compound was prepared by the method of Example 10 step n) using the product from step e). M.p. 181-182 °C.

^{1}H NMR 400MHz (d_6-DMSO) 8.53 (1H, s), 7.54 (2H, d), 7.38 (1H, t), 7.30 (1H, t), 7.00 (1H, s), 6.45 (1H, s), 5.12 (1H, m), 3.33 (3H, m), 2.64 (1H, m), 1.99 (1H, m), 1.85 (1H, m).

Example 17

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-ethyl-3-pyridinecarbonitrile ethanedioate

a) 2-Chloro-6-ethyl-3-pyridinecarbonitrile

To a stirred solution of 2-chloro-6-methyl-3-pyridinecarbonitrile (1.52 g) in dry DMF (10 ml) under a nitrogen atmosphere, was added iodomethane (2.5 ml). Sodium hydride (60% dispersion, 400 mg) was then added to the stirred solution. After the initial exothermic reaction subsided the mixture was stirred for 0.5 h then diluted with water (50 ml), and the products extracted with diethyl ether (100 ml). The dried extract ($MgSO_4$) was concentrated to dryness, and the residue was purified by chromatography (silica, isohexane/diethyl ether 4:1) to give the sub-title compound (700 mg).

^{1}H 400MHz ($CDCl_3$) 7.8 (1H, d), 7.16 (1H, d), 2.81 (2H, q), 1.26 (3H, t).

b) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-[(3-cyano-6-ethyl-2-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

A solution of the product from step a) (200 mg) and product from Example 1 step b) (442 mg) were stirred at ambient temperature in 7M ammonia in methanol (15 ml) for 2 h. The

mixture was then concentrated to dryness and the residue purified by chromatography (silica isohexane/diethyl ether 7:3) to afford the sub-title compound (260 mg).

MS APCI +ve $^{m}/z$ 468 ($[M+H]^{+}$)

c) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-ethyl-3-pyridinecarbonitrile ethanedioate

The title compound was prepared from the product from step b), according to the procedure described in Example 8 step c), and was isolated as a colourless solid 80 mg.

^{1}H 400MHz (DMSO-d_6) 8.09 (1H, d), 7.5 (2H, d), 7.37-7.19 (4H, m), 5.35 (1H, t), 3.58-3.44 (2H, m), 3.09-3.04 (2H, m), 2.85 (2H, q), 2.35-2.25 (2H, m), 1.26 (3H, t).
MS APCI +ve $^{m}/z$ 328 ($[M+H]^{+}$).

Example 18

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(1-methylethyl)-3-pyridinecarbonitrile ethanedioate

a) 2-[[(1*R*)-2-[(4*S*)-2,2-Dimethyl-4-oxazolidinyl]-1-phenylethyl]thio]-6-(1-methylethyl)-3-pyridinecarbonitrile

The sub-title compound was synthesised from 2-chloro-6-(1-methylethyl)-3-pyridinecarbonitrile according to the procedure described in Example 17 step b).

MS APCI +ve $^{m}/z$ 382 ($[M+H]^{+}$).

b) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(1-methylethyl)-3-pyridinecarbonitrile ethanedioate

The title compound was synthesised from the product from step a) according to the procedure described in Example 8 step c).

MS APCI +ve $^{m}/z$ 342 ($[M+H]^{+}$).

^{1}H 300MHz (DMSO-d_6) 8.1 (1H, d), 7.5-7.19 (6H, m), 5.37 (1H, t), 3.6-3.4 (2H, m), 3.16-3.0 (2H, m), 2.28 (2H, t), 1.27 (3H, d), 1.23 (3H, d).

Example 19

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinemethanol ethanedioate

a) Methyl 6-methyl-2-(methylsulfonyl)pyridine-3-carboxylate

A mixture of methyl 2-chloro-6-methylpyridine-3-carboxylate (1 g) and sodium methanesulphinate (1.6 g) in dry DMSO (10 ml) was heated at 120°C for 4 h. The cooled reaction mixture was diluted with water (100 ml) and the products extracted into ethyl acetate (2x100 ml). The dried extracts ($MgSO_4$) were concentrated to dryness and the residue purified by chromatography (silica, diethyl ether). The sub-title compound was isolated as a pale pink oil (600 mg).

MS APCI +ve $^m/z$ 230 ($[M+H]^+$).

b) Methyl 2-[[(1*R*)-2-[(4*S*)-3-[(1,1-dimethylethoxy)carbonyl]-2,2-dimethyl-4-oxazolidinyl]-1-phenylethyl]thio]-6-methyl pyridine-3-carboxylate

The sub-title compound was prepared from the product from step a according to the procedure described in Example 10 step m).

MS APCI +ve $^m/z$ 487 ($[M+H]^+$).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[[3-(hydroxymethyl)-6-methyl-2-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

A solution of the product from step b) (500 mg) in dry THF at ambient temperature, and under a nitrogen atmosphere was treated with lithiun borohydride (2M solution in THF 5x5 ml aliquots over 3 days). After 5 days the mixture was diluted with water (100 ml) and the excess reagent destroyed by addition of citric acid. The mixture was then extracted with

ethyl acetate (2x75 ml) and the combined extracts dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (silica diethyl ether/ isohexane 7:3) to afford the title compound as a colourless gum (400 mg).

MS APCI +ve $^{m}/z$ 459 ($[M+H]^+$).

d) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinemethanol ethanedioate

The title compound was prepared from the product from step c) according to the procedure described in Example 8 step c).

^{1}H 300MHz (DMSO-d_6/D_2O) 7.6-7.2 (6H, m), 6.97 (1H, d), 5.28 (1H, t), 4.36 (2H, s), 3.63-3.38 (2H, m), 3.15 (1H, t), 2.5 (3H, s), 2.31 (2H, t).
MS APCI +ve $^{m}/z$ 319 ($[M+H]^+$).

Example 20

6-Acetyl-2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridine carbonitrile Hydrochloride

a) 6-Acetyl-2-(methylsulfonyl)-3-pyridine carbonitrile

6-Acetyl-2-(methylthio)-3-pyridine carbonitrile (170mg) was dissolved in acetone (40 ml) and water (8ml). Oxone (1.66 g) was added and the suspension stirred at room temperature for 68 h. 0.5M aqueous sodium thiosulphate solution (50 ml) was added and the solution stirred for 0.5h. The reaction was then extracted with ethyl acetate (3 x 50 ml) and combined organic extracts washed with water (3x20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (silica, hexane/ethyl acetate as eluent) to give the sub-title compound (109mg) as a white solid.

^{1}H NMR 300MHz ($CDCl_3$) 8.40 (2H, dd), 3.47 (3H, s), 2.78 (3H, s).

b) (4S)-1,1-Dimethylethyl 4-[(2R)-2-[(6-acetyl-3-cyano-2-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product of step a) (100 mg) and the product of Example 10 step g) (199 mg). The product was purified by chromatography (silica, hexane/ethyl acetate as eluent) to give the sub-title compound (125 mg) as a colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.89 (1H, s), 7.71 (1H, d), 7.46 (2H, t), 7.32 (2H ,t), 7.23 (1H ,d), 5.16 (1H, m), 4.16 (1H, m), 3.86 (1H, m), 3.51 (1H, m), 2.75-2.62 (3H, d), 2.60-2.33 (1H, m), 2.23-2.10 (1H, m), 1.59-1.40 (15H, m).

c) 6-Acetyl-2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridine carbonitrile Hydrochloride

The product of step b) (125 mg) was dissolved in methanol (20 ml) and the solution treated with 4M HCl in dioxane (10 ml). The reaction was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the residue triturated with 20% ethyl acetate in hexane. The solid was filtered and dried to give the title compound (75 mg) as a pale yellow solid. M.p. 78 °C.

MS APCI +ve $^m/z$ 342 ($[M+H]^+$).

^{1}H NMR 300MHz (DMSO-D_6) 8.41 (1H, dd), 8.16 (3H, s), 7.76 (1H, dd), 7.58 (2H, d), 7.39 (2H, t), 7.30 (1H, m), 5.46 (1H, t), 5.35 (1H, t), 3.59-3.40 (2H, m), 3.07 (1H, s), 2.76 (3H, d), 2.34 (2H, t).

Example 21

2-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(hydroxymethyl)-3-pyridine carbonitrile (*E*)-butenedioate

a) 6-(Hydroxymethyl)-2-(methylthio)-3-pyridine carbonitrile

6-Formyl-2-(methylthio)nicotinonitrile (500 mg) was dissolved in ethanol (50 ml) and the solution treated with sodium borohydride (117 mg). The reaction was stirred at room temperature for 1 h and then quenched with water (50 ml). The reaction was concentrated *in vacuo* down to approximately 50 ml and then extracted with ethyl acetate (3x60 ml). Combined organic extracts were washed with water (2 x 40 ml), dried ($MgSO_4$) and evaporated in vacuo to give the sub-title compound (478 mg) as a white solid.

^{1}H NMR 300MHz ($CDCl_3$) 7.79 (1H, d), 7.07 (1H, d), 4.80 (2H, d), 3.18 (1H, t), 2.65 (3H, s).

b) 6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-(methylthio)-3-pyridine carbonitrile

The product from step a) (473 mg) was dissolved in dichloromethane (80 ml) and treated with imidazole (196 mg). The solution was cooled to 0 °C and *t*-BDMSCl (434 mg) added. The reaction was stirred at room temperature for 18 h and then quenched with water (50 ml). Extracted with ethyl acetate (3x60ml) and combined organic extracts washed with (2 x 40 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the sub-title compound (731 mg) as a white solid.

^{1}H NMR 300 MHz ($CDCl_3$) 7.79 (1H, d), 7.27 (1H, d), 4.80 (2H, s), 2.59 (3H, s), 0.98 (9H, s), 0.13 (6H, s).

c) 6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-(methylsulfonyl)-3-pyridine carbonitrile

The product from step b) (725 mg) was dissolved in acetone (80 ml), water (40 ml) and aqueous saturated sodium bicarbonate solution (20 ml). The suspension was treated with oxone (4.1g) and the reaction stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* to approximately 70ml and extracted with ethyl acetate (3 x 60 ml). Combined organic extracts were washed with water (3 x 40 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the sub-title compound (715 mg) as a white solid.

^{1}H NMR 300MHz ($CDCl_3$) 8.24 (1H, d), 7.91 (1H, d), 4.92 (2H, s), 3.35 (3H, s), 0.97 (9H, s), 0.16 (6H, s).

d) 1,1-Dimethylethyl (4S)-4-[(2R)-2-[[3-cyano-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-2-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product of step c) (222 mg) and the product of Example 10 step g) (300 mg). The product was purified by chromatography (silica, hexane/ethyl acetate as eluent) to give the sub-title compound (180 mg) as a colourless oil.

^{1}H NMR 300MHz ($CDCl_3$) 7.75 (1H, d), 7.39 (2H, d), 7.33-7.18 (4H, m), 5.20-5.00 (1H, m), 4.89-4.67 (2H, m), 4.17-4.04 (1H, m), 3.85 (1H, s), 3.72-3.42 (1H, m), 2.66-2.33 (1H, m), 2.17 (1H, dd), 1.57-1.39 (15H, m), 0.96 (9H, d), 0.14 (6H, d).

e) 2-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(hydroxymethyl)-3-pyridine carbonitrile (*E*)-butenedioate

The title compound was prepared, by the method of Example 10 step n) using the product of step d) (175mg), as an off-white solid (100mg). M.p. 147-149 °C.

^{1}H NMR 300MHz (d_6-DMSO) 8.17 (1H, d), 7.50 (2H, d), 7.39-7.23 (4H, m), 6.46 (2H, s), 5.33 (1H, t), 4.69 (2H, dd), 3.51-3.34 (2H, m), 2.83 (1H, t), 2.35-2.14 (2H, m).
MS APCI +ve $^m/z$ 330 ($[M+H]^+$).

Example 22

2-[[(1*R*, 3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile (*E*)-butenedioate

a) 1,1-Dimethylethyl (4*S*)- 4-[(2*R*)-2-[(3-cyano-2-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The product from Example 10 step g) (318 mg) was dissolved in 7M ammonia in methanol (40 ml) and 2-chloro-3-cyanopyridine (100 mg) added. The reaction was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue purified by chromatography (silica, ethyl acetate/hexane as eluent) to give the sub-title compound (200 mg) as a colourless oil.

MS APCI +ve $^{m}/z$ 440 ([M+H]$^{+}$).

b) 2-[[(1*R*, 3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile (*E*)-butenedioate

The title compound was prepared, by the method of Example 10 step n) using the product of step a) as an off-white solid (125 mg). M.p. 67-69 °C.

^{1}H NMR 300MHz d_6-(DMSO) 8.74 (1H, d), 8.21 (1H, dd), 7.50 (2H, d), 7.32 (4H, m), 6.46 (2H, s), 5.37 (1H, t), 3.53-3.33 (2H, m), 2.90-2.80 (1H, m), 2.36-2.17 (2H, m).
MS APCI +ve $^{m}/z$ 300 ([M+H]$^{+}$).

Example 23

(β^{1}*S*,δ^{1}*R*)- β-Amino-δ-[(2,5-dichloro-4-pyridinyl)thiobenzenebutanol] Hydrochloride

a) 2,5-Dichloro-4-(methylthio)-pyridine

To DMF (3.13 ml) in THF (20 ml), under nitrogen, at 0 °C, was added nBuLi (8.9 ml of a 2.5M solution in hexanes) dropwise and stirred for 15 min. The reaction mixture was added dropwise to a solution of 2,5-dichloropyridine (3 g) in THF (20 ml) at –78 °C. After 2 h, dimethyldisulfide (2.4 ml) was added and the reaction temperature was allowed to warm up to 0 °C. Water was added and the mixture was extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and evaporated to give the sub-title compound as a yellow solid, (3 g).

^{1}H NMR 400MHz ($CDCl_3$) 8.18 (1H, s), 7.02 (1H, s), 2.50 (3H, s).

b) 2,5-Dichloro-4-(methylsulfonyl)-pyridine

The sub-title compound was prepared by the method of Example 5 step b) using the product from Example 23 step a). White solid.

^{1}H NMR 300MHz ($CDCl_3$) 8.39 (1H, s), 7.91 (1H, s), 2.90 (3H, s).

c) (β^1S,δ^1R)- β-Amino-δ-[(2,5-dichloro-4-pyridinyl)thiobenzenebutanol]-Hydrochloride

The title compound was prepared by the method of Example 10 steps m & n) using the products from Example 23 step b) and Example 10 step g). Final purification was by reversed phase HPLC followed by treatment with HCl.

MS (APCI+ve) $^m/z$ 343 [M(+H)]$^+$.

^{1}H 400MHz (DMSO-d_6) 8.37 (1H, s), 8.08 (3H, bs), 7.58 (3H, m), 7.41 (2H, t), 7.33 (1H, tt), 3.54-3.50 (2H, m), 3.41 (1H, dd), 2.96 (1H, bs), 2.33-2.14 (2H, m).

Example 24

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-fluoro-6-methoxy-3-pyridinecarbonitrile-(*E*)-butenedioate

a) 2-Chloro-5-fluoro-6-methoxy-3-pyridinecarbonitrile

A solution of 2,6-dichloro-5-fluoro-3-pyridinecarbonitrile (2.33 g) and sodium methoxide (1.9 ml of a 25 wt. % solution in methanol) in DMF was heated at 50°C for 16 h. Further sodium methoxide (0.57 ml) was added and the heating continued for a further 48 h. Water was added and the mixture was extracted with diethyl ether. The combined organics were washed with water, dried (Na_2SO_4) and evaporated to give the sub-title compound as a white solid (2.08 g).

^{1}H NMR 300MHz ($CDCl_3$) 7.58 (1H, d), 4.11 (3H, s).

b) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-fluoro-6-methoxy-3-pyridinecarbonitrile-(*E*)-butenedioate

The title compound was prepared by the method of Example 10 steps m & n) using the products from Example 24 step a) and Example 10 step g).

MS (APCI+ve) $^{m}/z$ 348 $[M(+H)]^+$.

^{1}H 400MHz (DMSO-d_6) 8.20 (1H, d), 7.49 (2H, d), 7.36 (2H, t), 7.28 (1H, m), 5.28 (1H, dd), 4.13 (3H, s), 3.31 (2H, m), 2.67 (1H, m), 2.21 (1H, m), 2.08 (1H, m).

Example 25

4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(dimethylamino)-3-pyridinecarbonitrile (*E*)-2-butenedioate

a) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-*N*,*N*-dimethyl-2-pyridinamine

A mixture of the product from Example 10 step h) (2.1 g), 2.0 M dimethylamine/THF (80 ml) and toluene (80 ml) was heated at 120 °C in a sealed tube for 16 h. The mixture was then evaporated to dryness and the residue purified by chromatography (silica, ethyl acetate as eluent) to give the sub-title compound (1.55 g) as a pale orange solid.

^{1}H NMR 400MHz ($CDCl_3$) 8.64 (1H, s), 7.97 (1H, d), 6.48 (1H, d), 4.05 (2H, s), 3.14 (6H, s), 1.36 (6H, s).

b) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-*N*,*N*-dimethyl-4-(methylthio)-2-pyridinamine

The sub-title compound was prepared by the method of Example 10 step j) using the product from step a) and purified by chromatography (silica, isohexane/ethyl acetate as eluent).

MS APCI +ve $^{m}/z$ 266 ($[M(+H)]^+$).

c) 6-(Dimethylamino)-4-(methylthio)-3-pyridinecarbonitrile

The sub-title compound was prepared by the method of Example 10 step k) using the product from step b).

MS APCI +ve $^{m}/z$ 194 ([M(+H)]$^{+}$).

d) 6-(Dimethylamino)-4-(methylsulfonyl)-3-pyridinecarbonitrile,

The sub-title compound was prepared by the method of Example 16 step d) using the product from step c).

MS APCI +ve $^{m}/z$ 226 ([M(+H)]$^{+}$).

e) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[[5-cyano-2-(dimethylamino)-4- pyridinyl]thio]2-phenylethyl]-2,2-dimethyl-3-oxazolidincarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product from step d).

MS APCI +ve $^{m}/z$ 483 ([M(+H)]$^{+}$).

f) 4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(dimethylamino)-3-pyridinecarbonitrile (*E*)-2-butenedioate

The title compound was prepared by the method of Example 10 step n) using the product from step e). M.p. 175-177 °C

^{1}H NMR 400MHz (d_6-DMSO) 8.29 (1H, s), 7.55 (2H, d), 7.38 (2H, t), 7.29 (1H, t), 6.47 (4H, d), 5.11 (1H, m), 3.38 (2H, m), 3.05 (6H, s), 2.75 (1H, m), 2.17 (1H, m), 2.04 (1H, m).

Example 26

4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(methylamino)-3-pyridinecarbonitrile dihydrochloride

a) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-*N*-methyl-2-pyridinamine

A mixture of the product from Example 10 step h) (2.1 g), 2.0 M methylamine/THF (30 ml) and toluene (30 ml) was heated at 120 °C in a sealed tube for 16 h. The mixture was then evaporated to dryness and the residue purified by chromatography (silica, ethyl acetate as eluent) to give the sub-title compound (700 mg) as a beige solid.

^{1}H NMR 400MHz ($CDCl_3$) 8.60 (1H, s), 7.97 (1H, d), 6.36 (1H, d), 4.85 (1H, br s), 4.06 (2H, s), 2.96 (3H, d), 1.36 (6H, s).

b) 1,1-Dimethylethyl [5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-2-pyridinyl]methyl carbamate

Di-*tert*-butyl dicarbonate (1.47 g) was added to a solution of the product from step a) (700 mg) in dichloromethane (10 ml). 4-(Dimethylamino)pyridine (42 mg) was then added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured onto water and the organic phase separated, dried ($MgSO_4$), filtered and evaporated to dryness to give the sub-title compound (900 mg) as colourless oil.

MS APCI +ve $^m/z$ 306 ($[M(+H)]^+$).

c) 1,1-Dimethylethyl [5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-4-(methylthio)-2-pyridinyl]methyl- carbamate

The sub-title compound was prepared by the method of Example 10 step j) using the product from step b).

MS APCI +ve $^m/z$ 252 ($[M(+H)]^+$).

d) 1,1-Dimethylethyl [5-cyano-4-(methylthio)-2-pyridinyl]methyl carbamate

The sub-title compound was prepared by the method of Example 10 step k) using the product from step c).

MS APCI +ve $^m/z$ 180 ($[M(+H)]^+$).

e) 1,1-Dimethylethyl [5-cyano-4-(methylsulfonyl)-2-pyridinyl]methyl carbamate

The sub-title compound was prepared by the method of Example 16 step d) using the product from step d).

MS APCI +ve $^{m}/z$ 212 ($[M(+H)]^{+}$).

f) 1,1-Dimethylethyl (4*S*) 4-[[[5cyano[[(1,1dimethylethoxy)carbonyl]methylamino]-4-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl- 3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product from step e).

MS APCI +ve $^{m}/z$ 569 ($[M(+H)]^{+}$).

g) 4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-(methylamino)- 3-pyridinecarbonitrile dihydrochloride

To a solution of the product from step f) (490 mg) in methanol (20 ml), was added 4M HCl in dioxan (20 ml). The mixture was stirred at room temperature for 8 h and the solvent was removed *in vacuo*. The residue was triturated with diethyl ether and the title compound (340 mg) was collected by filtration as a white solid. M.p. 206-208 °C.

MS APCI +ve $^{m}/z$ 329 ($[M(+H)]^{+}$).

^{1}H NMR 400MHz (d_6-DMSO) 8.21 (1H, s), 8.18 (2H, br s), 7.53 (2H, m), 7.36 (2H, m), 7.28 (1H, m), 6.66 (1H, s), 5.04 (1H, t), 3.45 (2H, m), 2.99 (1H, br s), 2.83 (3H, s), 2.31 (2H, t).

Example 27

($\beta^{1}S,\delta^{1}R$)- β-Amino-δ-[(5-bromo-2-methoxy-4-pyridinyl)thio]-benzenebutanol (*E*)-2-butenedioate

a) 5-Bromo-2-methoxy-4-(methylthio)-pyridine

To *N,N*-diisopropylamine (11.7 ml) in THF (45 ml), under nitrogen, at 0 °C, was added nBuLi (32.5 ml of a 2.5M solution in hexanes) dropwise and stirred for 15 min. The reaction mixture was cooled to –78 °C and a solution of 5-bromo-2-methoxypyridine (14.3 g) in THF (10 ml) was added dropwise. After 2 h, dimethyldisulfide (13.8 ml) was added followed by THF (20 ml). The reaction temperature was allowed to warm up to -40 °C. The reaction was poured into aqueous ammonium chloride solution, and the mixture extracted with ether. The combined organics were dried (Na_2SO_4) and evaporated. Trituration with cold isohexane gave the sub-title compound as a beige solid, (11 g).

^{1}H NMR 300MHz ($CDCl_3$) 8.08 (1H, s), 6.45 (1H, s), 3.91 (3H, s), 2.44 (3H, s).

b) 5-Bromo-2-methoxy-4-(methylsulfonyl)pyridine

The sub-title compound was prepared by the method of Example 16 step d) using the product from step a).

MS APCI +ve $^m/z$ 267/269 ($[M(+H)]^+$).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(5-bromo-2-methoxy-4-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product from step b).

MS APCI +ve $^m/z$ 523/525 ($[M(+H)]^+$).

d) (β^1S,δ^1R)- β-Amino-δ-[(5-bromo-2-methoxy-4-pyridinyl)thio]- benzenebutanol (*E*)-2-butenedioate,

The title compound was prepared by the method of Example 10 step n) using the product from step c). M.p. 178-180 °C

MS APCI +ve $^m/z$ 383/385 ($[M(+H)]^+$).

^{1}H NMR 400MHz (d_6-DMSO) 8.17 (1H, s), 7.56 (2H, d), 7.38 (2H, t), 7.29 (1H, t), 6.86 (1H, s), 6.47 (2H, s), 4.98 (1H, m), 3.79 (3H, s), 3.30-3.41 (2H, m), 2.72 (1H, m), 2.17 (1H, m), 2.04 (1H, m).

Example 28

(β^1S,δ^1R) β-Amino-δ-[(5-chloro-2-methoxy-4-pyridinyl)thio]-benzenebutanol (*E*)-2-butenedioate

a) 5-Chloro-2-methoxy-4-(methylthio)-pyridine

The product from Example 23 step a) (1.4 g) in methanol (20 ml) was treated with sodium methoxide (8.2 ml of a 25wt% solution in methanol) and heated at reflux for 48 hrs. The solvent was removed under reduced pressure and the residue was partitioned between water (50 ml) and dichloromethane (50 ml). The organic phase was dried ($MgSO_4$) and evaporated to dryness. Purification by chromatography (silica, dichloromethane as eluent) gave the sub-title compound (345 mg) as a white solid.

MS APCI +ve $^{m}/z$ 189 ([M(+H)]$^{+}$).

b) 5-Chloro-2-methoxy-4-(methylsulfonyl)pyridine

The sub-title compound was prepared by the method of Example 5 step b) using the product from step a).

MS APCI +ve $^{m}/z$ 222/224 ([M(+H)]$^{+}$).

c) 1,1-Dimethylethyl (4*S*)- 4-[(2*R*)-2-[(5-chloro-2-methoxy-4-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 step m) using the product from step b).

MS APCI +ve $^{m}/z$ 479/481 ([M(+H)]$^{+}$).

d) ($\beta^1 S,\delta^1 R$)- β-Amino-δ-[(5-chloro-2-methoxy-4-pyridinyl)thio]- benzenebutanol (*E*)-2-butenedioate

The title compound was prepared by the method of Example 10 step n) using the product from step c). M.p. 191-193 °C.

MS APCI +ve $^m/z$ 339-341 ([M(+H)]$^+$)

^{1}H NMR 400MHz (d_6-DMSO) 8.08 (1H, s), 7.56 (2H, d), 7.38 (2H, t), 7.29 (1H, t), 6.88 (1H, s), 6.48 (2H, s), 4.99 (1H, m), 3.80 (3H, s), 3.30-3.41 (2H, m), 2.73 (1H, m), 2.18 (1H, m), 2.05 (1H, m).

Example 29

4-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-ethoxy-3-pyridinecarbonitrile, (*E*)-butenedioate

a) 5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-2-ethoxy-pyridine

The product from Example 10 step h) (2.1 g) in DMF (50 ml) was treated with ethanol (1.2 ml) and sodium hydride (0.8 g of a 60% dispersion in mineral oil) and heated at 60 °C for 20 h. Water (200 ml) was added and the resulting mixture was extracted with ethyl acetate (2 x 150 ml). The combined organics were dried ($MgSO_4$) and evaporated to give the sub-title compound as a yellow oil, (3.0 g).

MS APCI +ve $^m/z$ 221 [M+H]$^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.66 (1H , s), 8.09 (1H, d), 6.71 (1H, d), 4.40 (2H, q), 4.09 (2H, s), 1.26-1.41 (9H, m).

b) 6-Ethoxy-4-(methylthio)-3-pyridinecarbonitrile

The sub-title compound was prepared by the method of Example 10 steps j) to k) from the product from step a).

MS APCI +ve $^{m}/z$ 195 $[M+H]^{+}$.

^{1}H NMR 400MHz (d_6-DMSO) 8.28 (1H, s), 6.49 (1H, s), 4.42 (2H, q), 2.52 (3H, s), 1.38 (3H, t).

c) 6-Ethoxy-4-(methylsulfonyl)-3-pyridinecarbonitrile

The sub-title compound was prepared by the method from Example 14 step d) from the product from step b).

^{1}H NMR 400MHz (d_6-DMSO) 8.67 (1H, s), 7.44 (1H, s), 4.52 (2H, q), 3.27 (3H, s), 1.42 (3H, t)

d) 4-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-6-ethoxy-3-pyridinecarbonitrile (*E*)-butenedioate

The title compound was prepared by the method of Example 10 steps m) to n) using the product from step c). M.p. 169.5-171.5 °C.

MS APCI +ve $^{m}/z$ 344 $[M+H]^{+}$.

^{1}H NMR 400MHz (d_6-DMSO) 8.52 (1H, s), 7.55 (2H, d), 7.39 (2H, t), 7.30 (1H, t), 6.98 (1H, s), 6.47 (2H, s), 5.13 (1H, m), 4.34 (2H, q) 3.40 (2H, m), 2.70 (1H, m), 2.21 (1H, m), 2.02 (1H, m), 1.30 (3H, t).

Example 30

3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile Ethanedioate

a) 1,1-Dimethylethyl, (4*S*)-4-[(2*R*)-2-[[2-cyano-5-(trifluoromethyl)-3-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 1 step c), using the product from Example 1 step b) and 3-chloro-2-cyano-5-trifluoromethylpyridine.

MS APCI +ve $^{m}/z$ 408 $[M+H-Boc]^{+}$.

b) 3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)- 2-pyridinecarbonitrile ethanedioate

The title compound was prepared by the method of Example 1 step d), using the product of step a) to give the title compound as a white solid (133 mg). M.p. 147-149 °C.

MS APCI +ve $^{m}/z$ 368 $[M+H]^{+}$.

^{1}H NMR 400MHz (d_6-DMSO) 8.98 (1H, s), 8.33 (1H, s), 7.34 (5H, m), 5.04 (1H, t), 3.58 (1H, dd), 3.48 (1H, m), 3.05 (1H, m), 2.33 (1H, m), 2.18 (1H, m).

Example 31

3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-1,6-dihydro-5-methyl-6-oxo-2-pyridinecarbonitrile

a) 3-Bromo-5-methyl-2-pyridinecarbonitrile

A solution of 3-bromo-2-fluoro-5-methylpyridine (J. Het. Chem. 1967, 641, 642) in dry DMSO (100 ml) was treated with sodium cyanide (1.48 g) and heated to 80 °C for 24 h. The mixture was poured into brine, extracted with ethyl acetate and the organic layer dried ($MgSO_4$). The solvent was evaporated and the residue was purified by chromatography (silica, diethyl ether) to give the sub-title product as a pale yellow solid (3.0 g).

^{1}H NMR 400MHz ($CDCl_3$) 8.47 (1H, s), 7.84 (1H, s), 2.44 (3H, s).

b) 3-Bromo-5-methyl-2-pyridinecarbonitrile-N-oxide

A solution of the product from step a) (2.0 g) in glacial acetic acid (100 ml) was treated with 30% hydrogen peroxide (20 ml) and heated to 80 °C for 22 h. The mixture was evaporated, the residue triturated with hexane and the resulting solid collected to give the sub-title product as a pale yellow solid (2.0 g).

MS APCI +ve $^{m}/z$ 214 $[M+H]^+$.

^{1}H NMR 400MHz ($CDCl_3$) 8.07 (1H, s), 7.35 (1H, s), 2.37 (3H, s).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(2-cyano-5-methyl-3-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate N-oxide

The sub-title compound was prepared by the method of Example 1 step c), using the thiobenzoate of Example 1 step b) and the pyridine-N-oxide from step b) (0.43 g) to give a gum (1.25 g), which was used directly in step d).

MS APCI +ve $^{m}/z$ 470 $[M+H]^+$.

d) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[[6-(acetyloxy)-2-cyano-5-methyl-3-pyridinyl]thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate,

A solution of the product from step d) in acetic anhydride (20 ml) was heated under reflux for 4 h. The mixture was evaporated, the residue was dissolved in ethyl acetate and washed with water, then aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by chromatography (silica, 20% ethyl acetate/hexane) to give the sub-title product as a viscous oil (0.45 g).

MS APCI +ve $^{m}/z$ 456 $[M+2H\text{-}tBu]^+$.

e) 3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-1,6-dihydro-5-methyl-6-oxo-2-pyridinecarbonitrile

The title compound was prepared by the method of Example 1, step d), using the product of step d) to give the title compound as a white solid (131 mg), isolated as its free base.

MS APCI +ve $^{m}/z$ 330 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 7.27 (1H, s), 7.26 (5H, m), 4.53 (1H, m), 3.23 (4H, m), 2.50 (1H, m), 2.12 (1H, m), 1.82 (1H, m), 1.97 (3H, s).

Example 32

3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-2-pyridinecarbonitrile ethanedioate

The title compound was prepared by the method of Example 10 steps m & n) using 3,5-dichloro-2-pyridinecarbonitrile and the product from Example 10 step g). After treatment with HCl the title compound was purified by reversed phase HPLC (to remove an unwanted regioisomer) and then treated with ethanedioic acid to afford a white solid.

MS (APCI+ve) $^{m}/z$ 334 $[M(+H)]^+$.

^{1}H 400MHz (DMSO-d_6) 8.66 (1H, d), 8.22 (1H, d), 8.03 (ca. 2H, vbs), 7.41-7.27 (5H, m), 4.97 (1H, t), 3.55 (1H, dd), 3.44 (1H, dd), 3.02 (1H, m), 2.32 (1H, m), 2.16 (1H, dt).

Example 33

6-Amino-4-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile (*E*)-butenedioate

a) 1,6-Dihydro-4-(methylsulfonyl)-6-oxo-3-pyridinecarbonitrile

6-Methoxy-4-(methylsulfonyl)-3-pyridinecarbonitrile from Example 10 step l) (5.1 g) was dissolved in acetonitrile (200 ml) and sodium iodide (7.28 g) and trimethylsilylchloride (5.28 g) were added. The reaction was heated under reflux for 48 h and then cooled and the solvent evaporated *in vacuo*. The residue was partitioned between water (120 ml) and ethyl acetate (120 ml). After shaking, the layers were filtered and the solid collected and dried in a vacuum oven at 60 °C to give the sub-title compound as an off-white solid (3.6 g).

^{1}H NMR 400MHz (d_6-DMSO) 13.15 (1H, bs), 8.58 (1H, s), 6.89 (1H, s), 3.39 (3H, s).

b) 5-Cyano-4-(methylsulfonyl)-2-pyridinyl trifluoromethanesulfonate

Triflic anhydride (0.1 ml) was added to a solution of the product from step a) (57 mg) and triethylamine (0.1 ml) in acetonitrile (2 ml) at –20 °C and stirred at –20 °C to 20 °C for 2

h. Water was added and the mixture was extracted with dichloromethane. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, dichloromethane as eluent) to give the sub-title compound (66 mg).

^1H 300MHz ($CDCl_3$) 8.94 (1H, s), 7.91 (1H, s), 3.37 (3H, s).

c) 6-Amino-4-(methylsulfonyl)-3-pyridinecarbonitrile

0.5M Ammonia in dioxane (2 ml) was added to a solution of the product from step b) (164 mg) in THF (2 ml) and stirred for 16 h. The solvent was removed *in vacuo* and the residue purified by chromatography (silica, *iso*hexane/ethyl acetate as eluent) to give the sub-title compound (33 mg) as a white solid.

^1H NMR (d6-DMSO) 8.57 (1H, s), 7.78 (2H, s), 7.05 (1H, s), 3.35 (3H, s).

d) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(2-amino-5-cyano-4-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

A solution of the product from Example 10 step g) (105 mg) in 7 *M* ammonia in methanol (5 ml) was stirred for eight hours. The methanol was evaporated and the residue was dissolved in dry acetonitrile (3 ml). The product from step c) (45 mg) and caesium carbonate (151 mg) were added and the mixture was stirred at 20 °C for 1 h. Ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, *iso*hexane/acetone as eluent) gave the sub-title compound (55 mg) as a white solid.

MS (APCI+ve) $^m/z$ 455 $[M(+H)]^+$.

^1H 300MHz ($CDCl_3$) 8.16 (1H, s), 7.38-7.30 (5H, m), 6.83 (1H, s), 5.22 (2H, s), 4.45 (1H, d), 3.97 (1H, t), 3.55 (1H, t), 2.93 (1H, d), 2.59 (1H, d), 2.29 (1H, q), 1.61-1.42 (15H, m).

e) 6-Amino-4-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile (*E*)-butenedioate

The title compound was prepared from the product of step d) by the method of Example 10 step n).

MS (APCI+ve) $^{m}/z$ 315 [M(+H)]$^{+}$.

^{1}H NMR 400MHz (DMSO) 8.16 (1H, s), 7.51 (2H, d), 7.38 (2H, t), 7.31 (1H, t), 7.14 (2H, s), 6.62 (1H, s), 6.50 (2H, s), 4.95 (1H, s), 3.41-3.33 (2H, m), 2.78-2.70 (1H, m), 2.29-2.19 (1H, m), 2.16-2.07 (1H, m).

Example 34

3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-methyl-2-pyridinecarbonitrile

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(2-cyano-5-methyl-3-pyridinyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 1 step c), using the thiobenzoate of Example 1 step b) and the bromopyridine from Example 31 step a) (0.17 g) to give the product as a glass (0.19 g).

MS APCI +ve $^{m}/z$ 398 [M+2H-tBu]$^{+}$.

b) 3-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-methyl-2-pyridinecarbonitrile

The title compound was prepared by the method of Example 1 step d), using the product of step a) to give the title compound as a white solid (139 mg), isolated as its free base.

MS APCI +ve $^{m}/z$ 314 [M+H]$^{+}$.

^{1}H NMR 400MHz (d_6-DMSO) 8.41 (1H, s), 8.18 (2H, bs), 8.04 (1H, s), 7.43 (2H, d), 7.31 (3H, m), 5.32 (1H, bt), 5.13 (1H, m), 3.46 (2H, m), 2.93 (1H, m), 2.35 (3H, s), 2.28 (1H, m), 2.16 (1H, m).

Example 35

4-[[(1*R*,3*S*)-3-Amino-1-(2-fluorophenyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile Ethanedioate

a) 1,1-Dimethylethyl 4-[(2*S*)-2-(2-Fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate, and 1,1-Dimethylethyl 4-[(2*R*)-2-(2-Fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate

A stirred suspension of magnesium (243 mg) in THF (30 ml) under nitrogen was treated with 1,2-dibromoethane (2.44g) and warmed gently. An exotherm set in and the mixture began to reflux. After the metal had dissolved, the mixture was stored at room temperature under nitrogen. A stirred solution of 3-bromofluorobenzene (1.17g) in THF (10 ml) under nitrogen was treated at –65 to -70 °C with n-butyllithium (2.5 M in hexane, 2.26 ml, 5.67 mmol) and stirred at -70 °C for 30 min. The solution was treated at –65 to -70 °C with the solution of magnesium dibromide from above, stirred at -70 °C for 5 min, then at 0 °C for 20 min. A stirred solution of 1,1-dimethylethyl 2,2-dimethyl-4-[(4S)-2-oxoethyl)-3-oxazolidinecarboxylate (1.21 g) in THF (20 ml) under nitrogen was treated at 0 °C with the Grignard reagent formed above, stirred at 0 °C for 30 min, then at room temperature overnight. The solution was quenched with saturated aqueous ammonium chloride and extracted with ether. The washed and dried ($MgSO_4$) extracts were evaporated and the residue was purified by chromatography (silica, ether/isohexane as eluent) to give the sub-title compound 1,1-dimethylethyl 4-[(2*S*)-2-(2-Fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate as a white solid (600 mg).

^{1}H NMR 300MHz (d_4-MeOH) 7.38 (1H, s), 7.28 (4H, s), 7.12 (5H, d), 4.80-4.75 (9H, m), 4.00-3.79 (18H, m), 2.12-1.96 (11H, m), 1.54-1.41 (96H, m).

Further elution gave the second sub-title compound 1,1-Dimethylethyl 4-[(2R)-2-(2-Fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4S)-3-oxazolidinecarboxylate as a white solid (429 mg).

^{1}H NMR 300MHz (d_4-MeOH) 7.40-7.37 (1H, m), 7.28 (1H, s), 7.12 (1H, d), 4.83-4.79 (1H, m), 4.06 (1H, s), 3.90-3.84 (1H, m), 3.75-3.72 (1H, m), 2.20 (1H, s), 1.96-1.86 (1H, m), 1.54-1.47 (15H, m).

b) 4-Mercapto-6-methoxy-3-pyridinecarbonitrile,

A mixture of the product from Example 10, step I (1.0 g) and sodium hydrogen sulphide (790 mg) in ethanol (50 ml) was stirred for 2h and evaporated. The residue was taken up in water, treated with dilute hydrochloric acid until pH 6, and extracted with ethyl acetate. The dried (MgSO4) extracts were evaporated to give the sub-title compound as a tan powder (741 mg).

^{1}H NMR 300MHz ($CDCl_3$) 8.36 (1H, s), 6.72 (1H, s), 3.97 (3H, s).

c) 4-[[3(3S)-Amino-1(1R)-(2-fluorophenyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile Ethanedioate

A stirred solution of triphenylphosphine (309 mg) and THF (10 ml) under nitrogen was treated at –5 to 0 °C with DIAD (238 mg), stirred at –5 °C for 20 min, and then cooled to –20 °C and stored. A mixture of the product from step b) (196 mg), and the product from step a) (589 mg) were stirred, treated with the above DIAD/ triphenylphosphine solution, stirred overnight and evaporated. The residue was purified by chromatography (silica, ether/isohexane), taken up in methanol (10 ml), treated with 2M HCl in dioxan (10 ml), stirred for 2h and evaporated. The residue were purified by preparative reversed phase HPLC on a 19 x 50 mm Xterra C8 5 micron column using 10 to 60% acetonitrile in 2% aqueous 0.880 ammonia solution over 6 min at 20 ml/min. UV detection by DAD. The free base was taken up in ether/ ethanol mixture, treated with a solution of oxalic acid in ethanol and evaporated. The residue was triturated with ether and residue was dried to give the title compound as a cream powder (31 mg), M.p. 179-185 °C.

MS APCI +ve $^m/z$ 348 $[M+H]^+$.

^{1}H NMR 300MHz (d_4-MeOH) 8.58 (1H, s), 7.62 (1H, t), 7.43-7.37 (1H, m), 7.31-7.23 (2H, m), 6.98 (1H, s), 5.22 (1H, t), 3.91 (3H, s), 3.56-3.40 (4H, m), 3.05-3.02 (1H, m), 2.40-2.17 (2H, m).

Example 36

2-[[(1R,3S)-3-Amino-1-(4-fluorophenyl)-4-hydroxybutyl]oxy]-6-trifluoromethyl-3-pyridinecarbonitrile Ethanedioate

a) 1,1-Dimethylethyl 4-[(2*S*)-2-(4-Fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate, and 1,1-Dimethylethyl 4-[(2*R*)-2-(4-Fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate

A stirred solution of 1,1-dimethylethyl 2,2-dimethyl-4-[(4S)-2-oxoethyl)-3-oxazolidinecarboxylate (3.0 g) in THF (20 ml) under nitrogen was treated at 0 °C with 4-flurophenylmagnesium bromide (2M in ether, 8.32ml) and stirred at 0 °C for 1h. The solution was quenched with saturated ammonium chloride solution and extracted with ether. The washed and dried ($MgSO_4$) extracts were evaporated and the residue was purified by chromatography (silica, ether/isohexane as eluent) to give the sub-title compound 1,1-dimethylethyl 4-[(2*S*)-2-(4-fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate as a white solid (1.62g).

^{1}H NMR 300MHz (d_4-MeOH) 7.40-7.35 (2H, m), 7.10-7.04 (2H, m), 4.72-4.61 (1H, m), 4.02-3.74 (3H, m), 2.05-1.87 (2H, m), 1.55-1.41 (15H, m).

Further elution gave the second sub-title compound 1,1-dimethylethyl 4-[(2R)-2-(2-fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-(4S)-3-oxazolidinecarboxylate as a white solid (1.21g).

^{1}H NMR 300MHz (d_4-MeOH) 7.39 (2H, m), 7.07 (2H, m), 4.73-4.69 (1H, m), 4.08 (1H, m), 3.92-3.80 (2H, m), 2.15 (1H, m), 1.83 (1H, m), 1.53-1.41 (15H, m).

b) 2-[[(1*R*,3*S*)-3-Amino-1-(4-fluorophenyl)-4-hydroxybutyl]oxy]-6-trifluoromethyl-3-pyridinecarbonitrile Ethanedioate

A stirred solution of the 2R, 4S isomer from part a) (214mg) and 2-chloro-6-trifluoromethyl-3-pyridinecarbonitrile (130mg) in NMP (3ml) was treated with sodium hydride (60% dispersion in oil, 30mg), stirred overnight and evaporated. The residue was taken up in ether, washed, dried (MgSO4) and evaporated. The residue was purified by chromatography (silica, ether/isohexane as eluent) to give an oil that was taken up in methanol (5ml), treated with 4M HCl in dioxane, stirred for 2h and evaporated. The residues were purified by preparative reversed phase HPLC on a 19 x 50 mm Xterra C8 5 micron column using 10 to 80% acetonitrile in 2% aqueous 0.880 ammonia solution over 5 min at 20 ml/min. UV detection by DAD. The free base was taken up in ether/ ethanol mixture, treated with a solution of oxalic acid in ethanol and evaporated. The residue was triturated with ether and residue was dried to give the title compound as a cream powder (85 mg), M.p. 109-114 °C.

MS APCI +ve $^{m}/z$ 370 $[M+H]^+$.

^{1}H NMR 300MHz (d_4-MeOH) 8.34 (1H, d), 7.56-7.50 (3H, m), 7.13-7.09 (2H, m), 6.35-6.31 (1H, m), 3.85-3.81 (1H, m), 3.75-3.71 (1H, m), 3.53-3.47 (1H, m), 2.53-2.45 (1H, m), 2.34-2.27 (1H, m).

Example 37

2-(2*S*)-Amino-4-(4*R*)-(3-fluorophenyl)-4-[(4-methoxy-2-nitrophenyl)thio]butan-1-ol

a) 1,1-Dimethylethyl 4-[(2*S*)-2-(3-fluorophenyl)-2-hydroxyethyl]-2,2-dimethyl-3-(4*S*)-oxazolidinecarboxylate

The sub-title compound was prepared from 3-fluorophenylmagnesium bromide [from 3-fluorobromobenzene (2.91g), magnesium (485mg) and THF (20ml)] and 1,1-dimethylethyl 2,2-dimethyl-4-[(4S)-2-oxoethyl)-3-oxazolidinecarboxylate (3.0 g) by the method of Example 36, step a) to give a water-white oil (2.06g).

^{1}H NMR 300MHz (d_4-MeOH) 7.39-7.30 (1H, m), 7.18-7.09 (2H, m), 7.02-6.94 (1H, m), 4.75-4.63 (1H, m), 4.02-4.00 (2H, m), 3.76-3.72 (1H, m), 2.02-1.85 (2H, m), 1.55-1.42 (15H, m).

b) 1,1-Dimethylethyl 4-[(2-(benzoylthio)-2(2*R*)-(3-fluorophenyl)ethyl]-2,2-dimethyl-3(4*S*)-ozolidinecarboxylate

A stirred solution of triphenylphosphine (8.76g) in THF (100ml) under nitrogen was treated dropwise at 0 °C with DIAD (6.75g), stirred for 30min, treated with a mixture of thiobenzoic acid (4.61g) and the alcohol from part a) (5.67g), stirred overnight and evaporated. The residue was filtered through a pad of silica with dichloromethane/methanol and the filtrate was evaporated. The residue was digested with ether/isohexane and the supernatant was decanted off and evaporated. The residue was purified by chromatography (silica, dichloromethane/ *iso*hexane) to give the sub-title compound as a yellow oil (4.8g) that was used directly for the next stage.

c) 1,1-Dimethylethyl 4-[(2*R*)-2-(3-Fluorophenyl)-2-mercaptoethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate

A mixture of the product from step c) (4.8 g) and 7M methanolic ammonia was stirred for 6 h and evaporated to give the sub-title compound as a gum which was taken up in NMP (86 ml) and used directly for the next stage.

MS APCI +ve $^{m}/z$ 356 $[M+H]^+$.

d) 2-(2S)-Amino-4-(3-fluorophenyl)-4-(4R)-[(4-methoxy-2-nitrophenyl)thio]butan-1-ol

A mixture of caesium carbonate (717 mg) and 4-chloro-3-nitroanisole (0.2 mmol) was treated with the solution of the thiol from step d) (2ml) and stirred overnight. The mixture was diluted with water and extracted with methylene chloride. The washed and dried ($MgSO_4$) extracts were evaporated and the residue was purified by chromatography (silica, ether/isohexane) to give an oil that was taken up in methanol (2ml), treated with 4M HCl in dioxan (5 ml), stirred for 30 min and evaporated. The residue were purified by preparative reversed phase HPLC on a 19 x 50 mm Xterra C8 5 micron column using 10 to 60% acetonitrile in 2% aqueous 0.880 ammonia solution over 6 min at 20 ml/min. UV detection by DAD to give the title compound as a yellow oil (5 mg).

MS APCI +ve $^{m}/z$ 367 $[M+H]^+$.

^{1}H NMR 300MHz (d_4-MeOH) 7.44-7.38 (2H, m), 7.31-7.24 (1H, m), 7.16-7.05 (3H, m), 6.98-6.91 (1H, m), 4.65-4.60 (1H, m), 3.83 (3H, s), 3.50-3.35 (2H, m), 2.77-2.69 (1H, m), 2.16-2.06 (1H, m), 1.96-1.87 (1H, m).

Example 38

2(2S)-Amino-4(4R)-(3-fluorophenyl)-4-[(4-chloro-2-nitrophenyl)thio]butan-1-ol

The title compound was prepared from 1-bromo-4-chloro-2-nitrobezene and the thiol from Example 3, step c) (2 ml) by the method of Example 37 step d) as a yellow oil (14 mg).

MS APCI +ve $^m/z$ 371 $[M+H]^+$.
^{1}H NMR 300MHz (d_4-MeOH) 8.04-8.03 (1H, m), 7.63 (1H, d), 7.54 (1H, dd), 7.36-7.19 (3H, m), 7.01-6.94 (1H, m), 4.83-4.79 (1H, m), 3.46-3.34 (2H, m), 2.67-2.59 (1H, m), 2.17-2.06 (1H, m), 1.97-1.87 (1H, m).

Example 39

2(2S)-Amino-4(4R)-(3-fluorophenyl)-4-[(5-amino-4-chloro-2-nitrophenyl)thio]butan-1-ol

The title compound was prepared from 1-bromo-4-chloro-2-nitrobezene and the thiol from Example 37, step c) (2 ml) by the method of Example 37, step d) as a yellow oil (14 mg).

MS APCI +ve $^m/z$ 386 $[M+H]^+$.
^{1}H NMR 300MHz (d_4-MeOH) 8.13 (1H, s), 7.37-7.26 (3H, m), 7.03-6.96 (1H, m), 6.83 (1H, s), 4.71-4.66 (1H, m), 3.47-3.34 (2H, m), 2.69-2.61 (1H, m), 2.14-1.90 (2H, m).

Example 40

2(2S)-Amino-4(4R)-(3-fluorophenyl)-4-[(4-hydroxymethyl)-2-nitrophenyl)thio]butan-1-ol

The title compound was prepared from 1-bromo-4-chloro-2-nitrobezene and the product from Example 37, step c) (2 ml) by the method of Example 37, step d) as a yellow oil (12 mg).

MS APCI +ve $^{m}/z$ 367 $[M+H]^+$.
^{1}H NMR 300MHz (d_4-MeOH) 7.97 (1H, d), 7.61 (1H, d), 7.49 (1H, dd), 7.31-7.19 (3H, m), 6.98-6.91 (1H, m), 4.86-4.78 (1H, m), 4.61 (2H, s), 3.46-3.33 (2H, m), 2.68-2.60 (1H, m), 2.13-2.04 (1H, m), 1.97-1.87 (1H, m).

Example 41

2(2S)-Amino-4(4R)-(3-fluorophenyl)-4-[(4-fluoro-2-nitrophenyl)thio]butan-1-ol

The title compound was prepared from 1-chloro-4-fluoro-2-nitrobezene and the thiol from Example 37 step c) by the method of Example 37 step d).

MS APCI +ve m/z 355 [M+H]+.
^{1}H NMR 300MHz (d_4-MeOH) 7.79-7.74 (1H, m), 7.68-7.61 (1H, m), 7.39-7.26 (2H, m), 7.24-7.14 (2H, m), 7.01-6.93 (1H, m), 4.79-4.72 (1H, m), 3.47-3.35 (2H, m), 2.69-2.60 (1H, m), 2.16-2.05 (1H, m), 1.96-1.86 (1H, m).

Example 42

2(2S)-Amino-4(4R)-(3-fluorophenyl)-4-[(3,5-dichloro-2-pyridyl)thio]butan-1-ol

The title compound was prepared from 2,3,5-trichloropyridine and the thiol from Example 37 step c) (2ml) by the method of Example 37 step d) as a water-white oil (25 mg).

MS APCI +ve m/z 361 [M+H]+.

^{1}H NMR 300MHz (d_4-MeOH) 8.43 (1H, d), 7.82 (1H, d), 7.37-7.23 (3H, m), 7.02-6.95 (1H, m), 5.28-5.21 (1H, m), 3.48-3.34 (2H, m), 2.71-2.63 (1H, m), 2.26-2.16 (1H, m), 2.08-1.99 (1H, m).

Example 43

4-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-3-chlorobenzonitrile Ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(2-chloro-4-cyanophenyll)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound (320 mg) was prepared by the method of Example 3 step a) using the product from Example 1 step b) and 3-chloro-4-fluorobenzonitrile.

MS APCI +ve $^{m}/z$ 3473/5 (M+H^{+})

^{1}H NMR 400MHz (d_6-DMSO (90°C)) 7.87 (1H, d), 7.45-7.62 (4H, m), 7.23-7.34 (3H, m), 4.70 (1H, m), 4.04 (1H,m), 3.78 (1H,m), 3.65 (1H, m), 2.15 (1H, m), 2.06 (1H, m), 1.46 (9H, s), 1.43 (3H,s), 1.39 (3H, s).

b) 4-[[(1R,3S)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-3-chlorobenzonitrile Ethanedioate

The title compound (175 mg) was prepared as a white solid (M.p. 142 - 144 °C) by the method of Example 4 step b) using the product from step a).

MS APCI +ve $^{m}/z$ 333/5 (M+H^{+})

^{1}H NMR 400MHz (d_6-DMSO) 8.02 (1H, s), 7.75 (1H, d), 7.61 (1H, d), 7.52 (2H, m), 7.25-7.4 (3H, m), 5.00 (1H, m), 3.50 (1H, m), 3.39 (1H, m), 2.96 (1H, t), 2.10-2.30 (2H, m).

Example 44

4-Chloro-2-[[(1*R*,3*S*)-3-(ethylamino)-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-benzonitrile ethanedioate salt

To a solution of the product from Example 8 step c) (140 mg) in ethanol (4 ml) was added acetaldehyde (35 μl) and the reaction stirred for 16 h. After cooling to 0 °C, sodium borohydride (77 mg) was added and the reaction stirred for 30 min. Water (0.5 ml) was added and the mixture was diluted with ethyl acetate and filtered. The solution was dried ($MgSO_4$) and evaporated. Purification by reversed phase HPLC, neutralisation of relevant fractions and addition of ethanedioic acid (1 eq) gave the title compound. Recrystallisation from ethyl acetate / diethyl ether gave a white solid. M.p. 55-80 °C.

MS (APCI+ve) $^{m}/z$ 370 $[M(+H)]^+$.

^1H 400MHz (CD_3OD) 7.87 (1H, d), 7.70 (2H, m), 7.40 (1H, d), 6.05 (1H, dd), 3.92 (1H, dd), 3.80 (1H, dd), 3.51 (1H, m), 3.16 (2H, m), 2.54 (2H, m), 1.33 (3H, t).

Example 45

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]oxy]-5-fluoro-benzonitrile (2*E*)-2-butenedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-(2-chloro-5-thiazolyl)-2-hydroxyethyl]-2,2-dimethyl-3-oxazolidinecarboxylate and 1,1-dimethylethyl (4*S*)-4-[(2*S*)-2-(2-chloro-5-thiazolyl)-2-hydroxyethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

Butyl lithium (1.6 M in hexanes, 4.26 ml) was added dropwise to a solution of di*iso*propylamine (1.59 ml) in THF (20 ml) at –78 °C under a nitrogen atmosphere. After 15 minutes at –78 °C a solution of 2-chlorothiazole (900 mg) in THF (10 ml) was added dropwise and the reaction mixture was stirred cold for 15 minutes. A solution of 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate (1.82 g) in THF (10 ml) was then added over 5 minutes. After the addition was complete the cooling was removed and the mixture was stirred for 30 minutes. The reaction mixture was poured into

water and the products extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), filtered and evaporated under *vacuo*. Purification by chromatography (silica, 50% isohexane/diethyl ether as eluent) gave the (4*S*, 2*S*) sub-title compound (500 mg) as a colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.34 (1H, s), 5.47 (1H, d), 4.80 (1H, d), 4.32 (1H, m), 4.03 (1H, m), 3.73 (1H, d), 2.09 (1H, m), 1.89 (1H, m), 1.53 (15H, m).

Further elution gave the (4*S*, 2*R*) sub-title compound (380 mg) as a colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 7.37 (1H, s), 5.01 (1H, m), 4.73 (1H, br s), 4.18 (1H, br s), 4.05 (1H, m), 3.73 (1H, br d), 2.18 (2H, br d), 1.48 (15H, m).

<u>b) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-hydroxy-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate</u>

10% Palladium on charcoal was added to a solution of the product from step a) (380 mg) and sodium acetate (129 mg) in ethanol (15 ml). The reaction mixture was stirred under 5 atmospheres of hydrogen for 16 h. The mixture was filtered and evaporated. The residue was then dissolved in dichloromethane, re-filtered and evaporated to give the sub-title compound (235 mg) as a colourless oil.

^{1}H NMR 400MHz ($CDCl_3$) 8.73 (1H, br s), 7.76 (1H, s), 5.12 (1H, m), 4.22 (1H, m), 4.04 (1H, m), 3.82 (1H, m), 2.22 (2H, m), 1.48 (15H, s).

<u>c) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-(2-cyano-4-fluorophenoxy)-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate</u>

Caesium carbonate (466 mg) was added to a solution of the product from step b) (235 mg) and 2,5-difluorobenzonitrile (100 mg) in DMF (15 ml). The reaction mixture was then stirred at room temperature for 3 days. The reaction temperature was then increased to 55-60 °C for 5 days. After cooling to room temperature the mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* and the residue was purified by chromatography (silica,

*iso*hexane/ethyl acetate as eluent). The sub-title compound (150 mg) was obtained as a colourless oil.

MS APCI +ve $^{m}/z$ 448 ([M(+H)]$^{+}$).

d) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]oxy]-5-fluoro- benzonitrile (2*E*)-2-butenedioate

The title compound was prepared by the method of Example 10 step n) using the product from step c). M.p. 163-165 °C..

MS APCI +ve $^{m}/z$ 308 ([M(+H)]$^{+}$).

^{1}H NMR 400MHz (d_6-DMSO) 9.11 (1H, s), 8.04 (1H, s), 7.73 (1H, m), 7.52 (1H, m), 7.41 (1H, m), 6.47 (2H, s), 6.24 (1H, t), 3.55 (1H, m), 3.46 (1H, m), 3.00 (1H, t), 2.30 (1H, m), 2.17 (1H, m).

Example 46

2-[[(1*R*,3*S*)-3-Amino-4-methoxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

a) 6-Methyl-2-[[(1*R*)-1-phenyl-3-butenyl]thio]-3-pyridinecarbonitrile

A mixture of 2-mercapto-6-methyl-3-pyridinecarbonitrile (6.08 g), α-(2-propenyl)-(α^{1}*S*)-benzenemethanol (6 g) and triphenylphosphine (13.8 g) was stirred in dry THF (150 ml) at 0°C. To the mixture was added diisopropyl azodicarboxylate (10.4 ml) dropwise over 20 min. The mixture was then allowed to reach ambient temperature and stirred for 17 h. The reaction mixture was then concentrated to dryness and the residue purified by chromatography (silica isohexane/ethyl acetate 95:5) to afford the sub-title compound as a pale yellow oil (9.58 g).

MS APCI +ve $^{m}/z$ 281 ([M+H]$^{+}$).

b) 2-[[(1*R*,3*R*)-3,4-Dihydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile

AD-mix β (47.89 g) was added to a vigorously stirred mixture of 2-methyl-2-propanol and water (160 ml of each). The mixture was cooled to 0°C and the product from step a) (9.58 g) added dropwise to the mixture as a solution in 2-methyl-2-propanol (20 ml). After 20 h at 0°C the mixture was extracted with ethyl acetate (3x100 ml) and the organic extracts combined, dried (Na_2SO_4) and concentrated to dryness. The mixture was purified by chromatography (silica dichloromethane/7M ammonia in methanol 99:1 to 98:2) to give the sub-title compound (5.39 g).

MS APCI +ve $^{m}/z$ 315 ($[M+H]^+$).

<u>c) 2-[[(1*R*,3*R*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile</u>

Chloro-(1,1-dimethylethyl)dimethylsilane (1.54 g) was added to a stirred mixture of the product from step b) (3.2 g) and imidazole (700 mg) in dry THF (75 ml) at 0°C. The mixture was stirred at 0°C for 1 h and at 20 °C for 1 h. Extra chloro-(1,1-dimethylethyl)dimethylsilane (750 mg) and imidazole (350 mg) was added and stirring continued for a further 3 h. The mixture was concentrated to dryness and the residue dissolved in diethyl ether (100 ml) and the solution passed through a pad of silica gel. The ethereal solution was then concentrated to dryness to afford the sub-title (3 g).

MS APCI +ve $^{m}/z$ 429 ($[M+H]^+$).

<u>d) 2-[[(1*R*,3*R*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[(methylsulfonyl)oxy]-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile</u>

A solution of the product from step c) (5 g) in dry THF (50 ml) at 0 °C was treated with diisopropylethylamine (2.1 ml) and methanesulphonyl chloride (0.91 ml) and the mixture stirred for 1 h. A further 2 equivalents of diisopropylethylamine and methanesulphonyl chloride were added over the next 3 h to complete the reaction. The solvent was then removed under reduced pressure and the residue dissolved in a mixture of dichloromethane and diethyl ether (200 ml 1:1) and the solution passed through a pad of silica gel. The filtrate was collected and combined with further ether washes of the silica gel. Concentration gave the sub-title compound which was used immediately.

MS APCI +ve $^{m}/z$ 507 ([M+H]$^{+}$).

e) 2-[[(1*R*,3*S*)-3-Azido-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile

The product from step d) was dissolved in dry DMF (50 ml) and the solution treated with sodium azide (1.52 g). The mixture was heated to 90 °C for 4 h then cooled and diluted with water (100 ml). The products were extracted into diethyl ether (2x100 ml) and the combined extracts dried ($MgSO_4$) and concentrated to an oil. The crude product was purified by chromatography (silica diethyl ether/isohexane 1:4) to give the sub-title compound (4.9 g).

^{1}H NMR 400MHz ($CDCl_3$) 7.59 (1H, d), 7.43-7.2 (5H, m), 6.86 (1H, d), 5.29 (1H, dd), 3.65-3.54 (2H, m), 3.04 (1H, m), 2.56 (3H,s) 2.25-2.07 (2H, m), 0.83 (9h, s), 0.00(6H, s).

f) 2-[[(1*R*,3*S*)-3-Azido-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile

The product from step e) in dry THF (50 ml) containing tetrabutylammonium fluoride (11 ml, 1molar solution in THF) was stirred at ambient temperature for 20 h. The mixture was concentrated to dryness and the residue dissolved in a mixture of diethyl ether and dichloromethane then passed through a pad of silica gel. The filtrate was concentrated to give the sub-title compound (2.6 g).

MS APCI +ve $^{m}/z$ 454 ([M+H]$^{+}$).

g) 2-[[(1*R*,3*S*)-3-Azido-4-[(methylsulfonyl)oxy]-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile

An ice cold solution of the product from step f) (0.5 g) and diisopropylethylamine (0.26 ml) in dry THF(20 ml) was treated with methanesulphonyl chloride (0.12 ml). After the addition was complete the mixture was allowed to reach room temperature and stirred for 1 h. More diisopropylethylamine (0.26 ml) and methanesulphonyl chloride (0.12 ml) were added and stirring continued for a further 2 h. The mixture was diluted with water (100 ml) and the products extracted into ethyl acetate (2x50 ml). The combined organic extracts

were dried ($MgSO_4$) and concentrated to an oil. The crude product was purified by chromatography(silica, diethyl ether/isohexane 1:1). The sub-title compound was isolated as an oil (630 mg).

MS APCI +ve $^m/z$ 418 ([M+H]$^+$).

h) 2-[(3-Azido-4-methoxy-1-phenylbutyl)thio]-6-methyl-3-pyridinecarbonitrile

A solution of the sulfonate ester from step g) (0.9 g) in methanol (50 ml) was treated with sodium methoxide (1 ml 25wt/v solution in methanol) and the mixture refluxed for 20 h. The mixture was then concentrated to low volume and treated with 10% aqueous citric acid (20 ml). The products were extracted into diethyl ether (100 ml) and the extract dried ($MgSO_4$) and concentrated. The crude oil was purified by chromatography (silica, diethyl ether/isohexane 1:4) to afford the sub-title compound as an amber oil (200 mg).

MS APCI +ve $^m/z$ 354 ([M+H]$^+$).

i) 2-[[(1*R*,3*S*)-3-Amino-4-methoxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile

A solution of azide 46 g (198 mg) and triphenylphosphine in wet THF (10 ml + 0.2 ml water) was stirred and heated under reflux for 3 h. The mixture was then concentrated, and the residue purified by chromatography (silica, dichloromethane/7M ammonia in methanol 95:5) to afford the free base (180 mg). The ethanedioic acid salt was prepared by addition of 1 equivalent of ethanedioic acid in acetonitrile to the free base affording a cream coloured solid (180 mg).

MS APCI +ve $^m/z$ 328 ([M+H]$^+$).

^{1}H 400MHz (d_6-DMSO) 8.08 (1H, d), 7.51-7.19 6H, m), 5.31 (1H, t), 3.47-3.35 (2H, m), 3.21-3.17 (4H, m), 2.6 (3H, s), 2.33 (2H, t).

Example 47

<u>2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-4-methyl-1-phenylpentyl]oxy]-4-chloro-5-fluoro benzonitrile ethanedioate</u>

<u>a) 1,1-Dimethylethyl (4S) 4-[(2R)-2-hydroxy-2-phenylethyl]-2,2,5,5-tetramethyl-3-oxazolidinecarboxylate</u>

A solution of 1,1-dimethylethyl (4*S*)- 2,2,5,5-tetramethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate (4.6 g) in dry THF (50 ml) and under an atmosphere of nitrogen was treated at 0°C with phenylmagnesium bromide (1molar solution in THF 22 ml). After the addition was complete the reaction was allowed to warm to 20°C, and stirred for 0.5 h. The reaction mixture was quenched with aqueous citric acid (150 ml, 10% w/v), and the products extracted into ethyl acetate (2x75 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to a gum. The mixture of diastereomers was separated by chromatography (silica, *iso*hexane/diethyl ether). The title compound was isolated as a colourless solid (1.3 g).

^1H 400MHz (d_6-DMSO) 7.35-7.20 (5H, m), 5.19 (1H, d), 4.63-4.59 (1H, m), 3.93 (1H, m), 1.9-1.7 (2H, m), 1.50 (3H, s), 1.44 (9H, s), 1.29 (3H, s), 1.26 (3H, s), 1.24 (3H, s).

<u>b) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-(5-chloro-2-cyano-4-fluorophenoxy)-2-phenylethyl]-2,2,5,5-tetramethyl-3-oxazolidinecarboxylate</u>

The sub-title compound was prepared according to the procedure described in Example 8 step b), using the product of step a).

MS APCI +ve $^m/z$ 403 ([M+H-boc]$^+$).

<u>c) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-4-methyl-1-phenylpentyl]oxy]-4-chloro-5-fluoro benzonitrile ethanedioate</u>

The title compound was prepared from the compound from step b) by the method of Example 8 step c). M.p 80°C.

^1H 400MHz (d_6-DMSO) 7.62 (1H, d), 7.49-7.34 (5H, m), 7.17 (1H, d), 5.67 (1H, dd), 3.24 (1H, dd), 2.38-2.25 (2H, m), 1.26 (3H, s), 1.21 (3H, s).
MS APCI +ve $^m/z$ 363 ($[M+H]^+$).

Example 48

2-[[(1*S*,3*S*)-3-Amino-4-hydroxy-1-propylbutyl]oxy]-4-chloro-5-fluorobenzonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*) 4-[(2*S*)-2-hydroxypentyl]-2,2-dimethyl-3-oxazolidinecarboxylate
The sub-title compound was prepared by the method of Example 47 step a), but using propylmagnesium chloride and 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate.

MS APCI +ve $^m/z$ 188 ($[M+H\text{-boc}]^+$).

b) 1,1-Dimethylethyl (4*S*) 4-[(2*S*)-2-(5-chloro-2-cyano-4-fluorophenoxy)pentyl]-2,2-dimethyl-3-oxazolidinecarboxylate.
The sub-title compound was prepared by the method of Example 8 step b), using the product of step a) in dry THF.

MS APCI +ve $^m/z$ 341 ($[M+H\text{-boc}]^+$).

c) 2-[[(1*S*,3*S*)-3-Amino-4-hydroxy-1-propylbutyl]oxy]-4-chloro-5-fluorobenzonitrile ethanedioate
The title compound was prepared according to the procedure described for the product from Example 8 step c). M.p. 171-2°C

MS APCI +ve $^m/z$ 301 ($[M+H]^+$).

^{1}H 300MHz (d_6-DMSO) 8.02 (1H, d), 7.66 (1H, d), 4.79 (1H, m), 3.67-3.61 (1H, m), 3.48-3.42 (1H, m), 3.2 (1H, m), 1.92 (2H, t), 1.66-1.56 (2H, m), 1.5-1.2 (2H, m), 0.89 (3H, t).

Example 49

2-[[(1*S*)-1-[(2*S*)-2-Amino-3-hydroxypropyl]pentyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)- 4-[(2*R*)-2-hydroxyhexyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared in a similar procedure to that described for the compound from Example 47 step a), but using butylmagnesium chloride and 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate.

^{1}H 300MHz (d_6-DMSO) 4.53(1H, d), 4.28-4.22 (1H, m), 4.00 (1H, dd), 3.66 (1H, d), 3.55-3.42 (1H, m), 1.8-1.71 (1H, m), 1.5-1.3 (21H, m), 0.90 (3H, t).

b) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-(benzoylthio)hexyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 1 step b), but using the product from Example 49 step a).

MS APCI +ve $^m/z$ 322 ([M+H-boc]$^+$).

c) 1,1-Dimethylethyl (4*S*) 4-[(2*S*)-2-[(3-cyano-6-methyl-2-pyridinyl)thio]hexyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 17 step b), but using the product from Example 49 step b).

MS APCI +ve $^m/z$ 434 ([M+H]$^+$).

d) 2-[[(1*S*)-1-[(2*S*)-2-Amino-3-hydroxypropyl]pentyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

The title compound was prepared by the method of Example 8 step c) using the product of step c).

MS APCI +ve $^{m}/z$ 294 ([M+H]$^+$).

^{1}H 400MHz (d$_6$-DMSO) 8.09 (1H, d), 7.2 (1H, d), 4.22 (1H, br s), 3.5-3.8 (2H, m), 3.2 (1H, br s), 2.52 (3H, s), 1.5-2.2 (4H, m), 0.93 (4H,d), 0.88 (3H, t).

Example 50

2-[[(1*S*,3*S*)-3-Amino-4-hydroxy-1-(2-methylpropyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-hydroxy-4-methylpentyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 47 step a) but using isobutylmagnesium chloride and 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate.

MS APCI +ve $^{m}/z$ 202 ([M+H-boc]$^+$).

b) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-(benzoylthio)-4-methylpentyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 1 step b), but using the product from step a).

MS APCI +ve $^{m}/z$ 322 ([M+H-boc]$^+$).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-[(3-cyano-6-methyl-2-pyridinyl)thio]-4-methylpentyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 17 step b), but using the product from step b).

MS APCI +ve $^{m}/z$ 434 ([M+H]$^{+}$).

d) 2-[[(1*S*,3*S*)-3-Amino-4-hydroxy-1-(2-methylpropyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile ethanedioate

The title compound was prepared by the method of Example 8 step c), but using the product from step c).

MS APCI +ve $^{m}/z$ 322 ([M+H]$^{+}$).

^{1}H 400MHz (DMSO-d_6) 8.1 (1H, d), 7.2 (1H, d), 4.2-4.1 (1H, m), 3.7-3.5 (2H, m), 3.2 (1H, m), 2.52 (3H, s), 2.1-2 (1H, m), 1.73-1.7 (2H, m), 1.45-1.24 (4H, m), 0.86 (3H, t).

Example 51

2-[[(3*S*)-3-Amino-4-hydroxy-1-(5-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile (*E*)-butenedioate

a) (4*S*)-4-[2-(5-Isoxazolyl)-2-oxoethyl]-2-oxazolidinone

The sub-title compound was prepared by the method of Example 2 step a) using 5-isoxazolecarbonyl chloride.

^{1}H NMR (d6-DMSO) δ 8.84 (1H, d), 7.72 (1H, d), 4.49 (1H, t), 4.37 (1H, t), 4.24 (1H, quintet), 4.06 (1H, dd), 3.92-3.74 (2H, t)

b) (4*S*)-4-[2-Hydroxy-2-(5-isoxazolyl)ethyl]-2-oxazolidinone

The sub-title compound was prepared by the method of Example 2 step b) using the product of step a).

^{1}H NMR (d6-DMSO) 8.49 (1H, t), 7.83 & 7.65 (1H, s), 6.37 (1H, dd), 5.90 (1H, dd), 4.87 (1H, dd), 4.43-4.31 (1H, m), 4.10-3.72 (2H, m), 1.99-1.85 (2H, m)

c) (4*S*)-4-[2-(Benzoylthio)-2-(5-isoxazolyl)ethyl]-2-oxazolidinone

The sub-title compound was prepared by the method of Example 2 step c) using the product of step b).

MS APCI +ve $^{m}/z$ 318 $[M+H]^+$.

d) 2-[[1-(5-Isoxazolyl)-2-[(4*S*)-2-oxooxazolidinyl]ethyl]thio]-6-methyl-3-pyridinecarbonitrile

The sub-title compound was prepared by the method of Example 2 step d) using the product of step c).

MS APCI +ve $^{m}/z$ 330 $[M+H]^+$.

e) 1,1-Dimethylethyl (4*S*)-4-[2-[(3-cyano-6-methyl-2-pyridinyl)thio]-2-(5-isoxazolyl)ethyl]-2-oxo-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 2 step e) using the product of step d).

^{1}H NMR ($CDCl_3$) 8.22 (1H, ddd), 7.75 (1H, dd), 7.03 (1H, dd), 6.44 & 6.29 (1H,2 x dd), 5.59 & 5.48-5.40 (1H, t & m), 4.56-4.22 (3H, m), 2.65-2.54 (5H, m), 1.62-1.48 (9H, m)

f) 1,1-Dimethylethyl [(1*S*)-3-[(3-cyano-6-methyl-2-pyridinyl)thio]-1-(hydroxymethyl)-3-(5-isoxazolyl)propyl]carbamate

The sub-title compound was prepared by the method of Example 2 step f) using the product of step e).

MS APCI +ve $^{m}/z$ 405 $[M+H]^+$.

g) 2-[[(3*S*)-3-Amino-4-hydroxy-1-(5-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile, (*E*)-butenedioate

A solution of the product from step f) (48 mg) in 4M HCl in dioxane (2 ml) was stirred for 2 h. 2M Potassium carbonate solution was added and the mixture was as extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), evaporated and purified by chromatography (silica dichloromethane/7M ammonia in methanol as eluent) then converted into the (*E*)-butenedioate salt by addition of one equivalent of fumaric acid to give the title compound (17mg) as a white solid. M.p. 150-2 °C.

MS APCI +ve $^m/z$ 305 $[M+H]^+$

^{1}H NMR (d6-DMSO) 8.51 (1H, d), 8.13 (1H, d), 7.24 (1H, dd), 6.54 (1H, dd), 6.43 (2H, s), 5.69 & 5.62 (1H, 2 x t), 3.57-3.32 (3H, m), 2.97-2.75 (1H, m), 2.60 (3H, s), 2.43-2.01 (2H, m).

Example 52

2-[[(3*S*)-3-Amino-4-hydroxy-1-(5-isoxazolyl)butyl]oxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile, (*E*)-butenedioate

a) 2-[1-(5-Isoxazolyl)-2-[(4*S*)-2-oxo-4-oxazolidinyl]ethoxy]-6-(trifluoromethyl)- 3-pyridinecarbonitrile

Caesium carbonate (1.35 g) was added to a solution of the product of Example 51 step b) (330 mg) and 3-chloro-5-(trifluoromethyl)-2-pyridinecarbonitrile (556 mg) in DMF (2 ml) and the mixture was stirred at 20 °C for 1 h. Ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), evaporated and purified by chromatography (silica, *iso*hexane/ethyl acetate as eluent) gave the sub-title compound (258 mg).

^{1}H NMR ($CDCl_3$) 8.25 (1H, d), 8.15 (1H, t), 7.47 (1H, t), 6.53 (1H, t), 6.42 (1H, d), 5.78 &, 5.64 (1H, 2 x s), 4.66-4.53 (1H, m), 4.29-4.07 (2H, m), 2.68-2.37 (2H, m)

b) 1,1-Dimethylethyl (4*S*)-4-[2-[[3-cyano-6-(trifluoromethyl)-2-pyridinyl]oxy]-2-(5-isoxazolyl)ethyl]-2-oxo-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 2 step e) using the product of step a).

^{1}H NMR ($CDCl_3$) 8.24 (1H, d), 8.14 (1H, d), 7.46 (1H, d), 6.58 (1H, dd), 6.45 (1H, d), 4.57-4.39 (3H, m), 2.88-2.76 (1H, m), 2.68-2.57 (1H, m), 1.57-1.51 (9H, m)

c) 1,1-Dimethylethyl [(1*S*)-3-[[3-cyano-6-(trifluoromethyl)-2-pyridinyl]oxy]-1-(hydroxymethyl)-3-(5-isoxazolyl)propyl]-1-carbamate

The sub-title compound was prepared by the method of Example 2 step f) using the product of step b).

MS APCI +ve $^m/z$ 443 $[M+H]^+$

d) 2-[[(3S)-3-Amino-4-hydroxy-1-(5-isoxazolyl)butyl]oxy]-6-(trifluoromethyl)- 3-pyridinecarbonitrile, (*E*)-butenedioate

The title compound was prepared by the method of Example 51, step g) using the product of step c) using. M.p. 150-2 °C.

MS APCI +ve $^m/z$ 343 $[M+H]^+$

^{1}H NMR (DMSO) 8.63 (1H, d), 8.57 (1H, d), 7.74 (1H, d), 6.60 (1H, d), 6.55 (1H, t), 6.47 (2H, s), 3.64-3.49 (2H, m), 3.17-3.09 (1H, m), 2.38 (2H, t).

Example 53

2-[[3-(3*S*)-Amino-4-hydroxy-1-(1*R*)-(2-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile Ethanedioate

a) 1,1-Dimethylethyl 4-[(2*R*)-2-Hydroxy-2-(2-thienyl)ethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate

The sub-title compound was prepared from 2-bromothiophene (2.71 g), magnesium (485 mg) and 1,1-dimethylethyl 2,2-dimethyl-4-[(4*S*)-2-oxoethyl)-3-oxazolidinecarboxylate (3 g) in THF (20 ml) by the method of Example 36, part a) to give an oil (1.51g).

^{1}H NMR 300MHz (d_4-MeOH) 7.31 (1H, dd), 7.03-6.95 (2H, m), 5.00-4.95 (1H, m), 4.15-4.04 (1H, m), 3.92-3.86 (1H, m), 3.81-3.69 (1H, m), 2.35-2.18 (1H, m), 2.01-1.90 (1H, m), 1.56-1.44 (15H, m).

b) 2-[[3-(3*S*)-Amino-4-hydroxy-1-(1*R*)-(2-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile Ethanedioate

The title compound was prepared from the product from step a) (236 mg) and 4-chloro-2,5-difluorobenzonitrile by the method of Example 36, step b) to give a cream powder (38 mg).

MS APCI +ve $^m/z$ 341 $[M+H]^+$.

^{1}H NMR 300MHz (d_4-MeOH) 7.63 (1H, d), 7.47 (1H, d), 7.38 (1H, d), 7.24 (1H, d), 7.04-7.01 (1H, m), 6.00 (1H, dd), 3.87 (1H, dd), 3.75-3.69 (1H, m), 3.63-3.55 (1H, m), 2.58-2.48 (1H, m), 2.40-2.31 (1H, m).

Example 54

2-[[3-(3*S*)-Amino-4-hydroxy-1(1*R*)-(3-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile Ethanedioate

a) 1,1-Dimethylethyl 4-[(2*R*)-2-hydroxy-2-(3-thienyl)ethyl]-2,2-dimethyl-(4*S*)-3-oxazolidinecarboxylate

The sub-title compound was prepared from 3-bromothiophene (1.09 g), 1,1-dimethylethyl 2,2-dimethyl-4-[(4*S*)-2-oxoethyl)-3-oxazolidinecarboxylate (3 g) in THF (20 ml), and magnesium dibromide by the method of Example 35, step a) to give a yellow oil (158 mg).

^{1}H NMR 300MHz (d_4-MeOH) 7.40-7.37 (1H, m), 7.28 (1H, s), 7.12 (1H, d), 4.84-4.79 (1H, m), 4.13-3.97 (1H, m), 3.91-3.83 (1H, m), 3.77-3.69 (1H, m), 2.31-2.11 (1H, m), 1.97-1.84 (1H, m), 1.56-1.47 (15H, m).

b) 2-[[3(3S)-Amino-4-hydroxy-1(1R)-(3-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile Ethanedioate

The title compound was prepared from the alcohol prepared in step a) (158 mg) and 4-chloro-2,5-difluorobenzonitrile by the method of Example 36, step b) to give a cream powder (30 mg) M.p. 111-115 °C.

MS APCI +ve $^m/z$ 341 $[M+H]^+$.
^{1}H NMR 300MHz (d_4-MeOH) 7.62 (1H, d), 7.51-7.48 (2H, m), 7.25 (1H, d), 7.18-7.16 (1H, m), 5.78-5.75 (1H, m), 3.86 (1H, dd), 3.72-3.67 (1H, m), 3.58-3.53 (1H, m), 2.47-2.40 (1H, m), 2.29-2.23 (1H, m).

Example 55

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-(trifluoromethyl)benzonitrile dihydrochloride

a) 1,1-Dimethylethyl (4*S*)-4-[(2*S*)-2-hydroxy-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate and 1,1-Dimethylethyl (4*R*)-4-[(2*S*)-2-hydroxy-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compounds were prepared by the method of Example 1 step a) using 3-pyridylmagnesium bromide.

Initial elution of the column gave (2*S*, 4*S*) sub-title compound as an oil (3.40 g).

MS APCI +ve $^m/z$ 323 ($[M+H]^+$).

^1H NMR 400MHz ($CDCl_3$) 8.58 (1H, m), 8.49 (1H, d), 7.75 (1H, d), 7.26 (1H, m), 5.19 (1H, m), 4.68 (1H, m), 4.35 (1H, m), 4.03 (1H, m), 3.67 (1H, d), 2.03 (1H, m), 1.80 (1H, m), 1.62 (3H, s), 1.53 (12H, m).

Further elution of the column gave (2*R*, 4*S*) sub-title compound as a pale yellow oil (2.30 g).

MS APCI +ve $^m/z$ 323 ([M+H]$^+$).
^1H NMR 400MHz ($CDCl_3$) 8.59 (1H, m), 8.51 (1H, d), 7.73 (1H, d), 7.26 (1H, m), 4.83 (1H, m), 3.80-4.20 (4H, m), 2.07 (2H, m), 1.65 (3H, s), 1.50 (12H, m).

b) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-(benzoylthio)-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound (2.80 g) was prepared by the method of Example 2 step c) using the (2S,4S) product from step a).

MS APCI +ve $^m/z$ 443 (M+H$^+$).
^1H NMR 400MHz ($CDCl_3$) 8.68 (1H, d), 8.51 (1H, m), 7.91 (2H, m), 7.72 (1H, m), 7.55 (1H, m), 7.42 (2H, m), 7.26 (1H, m), 4.78 (1H, m), 3.90-4.15 (3H, m), 2.58-2.38 (1H, m), 2.13 (1H, m), 1.60-1.40 (15H, m).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[[2-cyano-5-(trifluoromethyl)phenyl]thio]-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound (180 mg) was prepared by the method of Example 3 step a) using the product from step b) and 2-fluoro-4-(trifluoromethyl)benzonitrile.

MS APCI +ve $^m/z$ 508 (M+H$^+$).

d) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-(trifluoromethyl)benzonitrile dihydrochloride

The product from step c) (175 mg) was stirred with methanol (5 ml) and 4 M hydrogen chloride in dioxane (5 ml) for 4 h. The reaction mixture was evaporated and the residue recrystallised from ethanol/diethyl ether to give the title compound (120 mg) as a white solid. M.p. 238-40 °C.

MS APCI +ve $^{m}/z$ 368 $[M+H]^+$.
^{1}H NMR 400MHz (d_6-DMSO) 8.90 (1H, s), 8.70 (1H, d), 8.40 (1H, m), 8.30 (2H, m), 8.05 (2H, m), 7.78 (2H, m), 5.47 (1H, m), 3.50-3.60 (2H, m), 3.03 (1H, m), 2.40 (2H, m), 2.30 (1H, m).

Example 56

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(5-pyrimidyl)butyl]thio]-4-chlorobenzonitrile hydrochloride

a) 1,1-Dimethylethyl 4-[(2*S*)-2-hydroxy-2-(3-pyridinyl)ethyl]-2,2-dimethyl- (4*S*)-3-oxazolidinecarboxylate and 1,1-Dimethylethyl 4-[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]-2,2-dimethyl- (4*S*)-3-oxazolidinecarboxylate

To a stirred solution of 1,1-dimethylethyl (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylate (4.55 g) and 5-bromopyrimidine (3.00 g) in dry THF (50 ml) at -78 °C and under nitrogen was added butyllithium (2.5M in hexanes, 7.90 ml) dropwise. The mixture was stirred at –78 °C for 1.5 hours then quenched with saturated ammonium chloride solution and the products extracted into ethyl acetate. The organic extract was dried ($MgSO_4$) and concentrated to an oil. The crude mixture of diastereomers was purified by chromatography (silica, methanol/dichloromethane as eluent).
Initial elution of the column gave the (2S,4S) sub-title compound as a yellow solid (1.08 g).

MS APCI +ve $^{m}/z$ 324 ($[M+H]^+$).

^{1}H NMR 400MHz ($CDCl_3$) 9.13 (1H, s), 8.76 (2H, s), 5.41 (1H, m), 4.67 (1H, m), 4.38 (1H, m), 4.06 (1H, dd), 3.68 (1H, d), 2.04 (1H, m), 1.79 (1H, m), 1.62 (3H, s), 1.55 (3H, s), 1.53 (9H, s).

Further elution of the column gave the (2R,4S) sub-title compound as a pale yellow oil (540 mg).

MS APCI +ve $^m/z$ 324 ([M+H]$^+$).
^{1}H NMR 400MHz ($CDCl_3$) 9.13 (1H, s), 8.77 (2H, s), 4.87 (1H, m), 4.67 (1H, m), 4.22 (1H, m), 3.85 (1H, m), 2.15 (2H, m), 1.48-1.60 (15H, m).

b) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-(benzoylthio)-2-(5-pyrimidinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 2 step c) using the (2*S*,4*S*) product from step a).

MS APCI +ve $^m/z$ 444 (M+H$^+$).
^{1}H NMR 400MHz ($CDCl_3$) 9.11 (1H, s), 8.81 (2H, m), 7.90 (2H, d), 7.58 (1H, m), 7.44 (2H, m), 4.76 (1H, m), 3.96 (2H, m), 2.40-2.65 (1H, m), 2.16 (1H, m), 1.45-1.80 (16H, m).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(5-chloro-2-cyanophenyl)thio]-2-(5-pyrimidinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound (200 mg) was prepared by the method of Example 3 step a) using the product from step b) and 4-chloro-2-fluorobenzonitrile.

MS APCI +ve $^m/z$ 475/7 (M+H$^+$).

d) 2-[[(1R,3S)-3-Amino-4-hydroxy-1-(5-pyrimidyl)butyl]thio]-4-chlorobenzonitrile hydrochloride

The title compound (90 mg) was prepared as a solid (m.p. 120-30 °C) by the method of Example 7 step c) using the product from step c).

MS APCI +ve $^{m}/z$ 335/7 $[M+H]^+$.
^{1}H NMR 400MHz (d_6-DMSO) 9.08 (1H, s), 8.85 (2H, s), 8.23 (3H, bs), 7.90 (1H, d), 7.84 (1H, d), 7.56 (1H, dd), 5.24 (1H, m), 3.50-3.75 (2H, m), 3.01 (1H, m), 2.43 (1H, m), 2.28 (1H, m).

Example 57

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-chloro-5-fluorobenzonitrile dihydrochloride

a) *O*-(5-Chloro-2-cyano-4-fluorophenyl) dimethylcarbamothioate
A solution of phenol (2.00 g), potassium carbonate (1.85 g) and *N,N*-dimethylthiocarbamate in acetone (30 ml) was heated to reflux for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (silica, *iso*hexane/diethyl ether as eluent) to give the sub-title compound as a solid (2.36 g).

MS APCI +ve $^{m}/z$ 259/261 $[M+H]^+$.
^{1}H NMR 400MHz ($CDCl_3$) 7.43 (1H, d), 7.36 (1H, d), 3.46 (3H, s), 3.40 (3H, s).

b) *S*-(5-Chloro-2-cyano-4-fluorophenyl) dimethylcarbamothioate
The product from step a) (2.35 g) was heated under reflux under nitrogen in dimethylaniline (25 ml) for 4 hours. The mixture was then poured into 2M HCl solution and extracted with ethyl acetate 3 times. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to leave the sub-title compound as a white solid (2.3 g).

^{1}H NMR 400MHz ($CDCl_3$) 7.73 (1H, d), 7.52 (1H, d), 3.13 (3H, s), 3.06 (3H, s).

c) 4-Chloro-5-fluoro-2-mercaptobenzonitrile

The product from step b) (2.00 g) was dissolved in methanol (100 ml) and a solution of sodium hydroxide (1.55 g) in water (50 ml) added. The mixture was heated to reflux under nitrogen for 1.5 hours. After cooling the mixture was evaporated and the residue diluted with water and then washed twice with diethyl ether. The aqueous layer was acidified with 2M HCl solution and extracted with ethyl acetate twice. The combined organice extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the sub-title compound (1.45 g).

^{1}H NMR 400MHz ($CDCl_3$) 7.50 (1H, d), 7.40 (1H, d), 4.08 (1H, s).

d) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(5-chloro-2-cyano-4-fluorophenyl)thio]-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The product from step c) (100 mg) was dissolved in THF (10 ml) and the (2S,4S) product from Example 55 step a) (170 mg) added followed by triphenylphosphine (140 mg) and diethyl azodicarboxylate (0.10 ml). The mixture was stirred at 20 °C for 24 hours and then evaporated. The residue was purified by chromatography (silica, diethyl ether as eluent) to give the sub-title compound as an oil (85 mg).

MS APCI +ve $^m/z$ 492/494 $[M+H]^+$.

e) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-chloro-5-fluorobenzonitrile dihydrochloride

The title compound (60 mg) was prepared as an off-white solid by the method of Example 55 step d) using the product from step d). M.p. 252-5 °C.

MS APCI +ve $^m/z$ 352/4 $[M+H]^+$.

^{1}H NMR 400MHz (d_6-DMSO) 8.78 (1H, s), 8.67 (1H, d), 8.20 (1H, d), 8.08 (2H, m), 7.72 (1H, dd), 5.21 (1H, t), 3.61-3.37 (2H, m), 3.03 (1H, m), 2.40 (1H, m), 2.25 (1H, m).

Example 58

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(3-pyridyl)butyl]thio]-4-bromobenzonitrile dihydrochloride

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(5-bromo-2-cyanophenyl)thio]-2-(3-pyridinyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound (170 mg) was prepared by the method of Example 3 step a) using the product from Example 55 step b) and 4-bromo-2-fluorobenzonitrile.

MS APCI +ve $^{m}/z$ 520/2 ($M+H^{+}$).

^{1}H NMR 400MHz ($CDCl_3$) 8.50-8.30 (1H, m), 7.75-7.57 (5H,m), 7.26 (1H, m), 4.50-3.60 (4H, m), 2.60-2.30 (1H, m), 2.18 (1H, m), 1.60-1.40 (15H, m).

b) 2-[[(1R,3S)-3-Amino-4-hydroxy-1-(3-pyridyl)butyl]thio]-4-bromobenzonitrile dihydrochloride

The title compound (118 mg) was prepared as a white solid by the method of Example 55 step d) using the product from step a). M.p. 278-280 °C.

MS APCI +ve $^{m}/z$ 380 $[M+H]^{+}$.

^{1}H NMR 400MHz (d_6-DMSO) 8.94 (1H, s), 8.73 (1H, d), 8.42 (1H, d), 8.32 (3H, bs), 8.03 (1H, s), 7.84 (1H, dd), 7.74 (1H, d), 7.68 (1H, dd), 5.41 (1H, m), 3.60-3.48 (2H, m), 3.02 (1H, m), 2.43 (1H, m), 2.27 (1H, m).

Example 59

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-6-methyl-3-pyridinecarbonitrile hydrochloride

a) Bis(1,1-dimethylethyl) 2-(6-chloro-5-cyano-3-fluoro-2-pyridinyl)propanedioate

To a solution of bis(1,1-dimethylethyl) malonate (1.08 g) in dry DMF (20 ml) was added sodium hydride (200 mg) under nitrogen. The mixture was stirred at 20 °C for 30 minutes then 2,6-dichloro-3-cyano-5-fluoropyridine added. The mixture was stirred for 30 minutes

then poured into glacial acetic acid (100 ml) and extracted into ether. The ether layer was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography (silica, dichloromethane/*iso*hexane as eluent) to give the sub-title compound as a solid (1.38 g).

MS APCI +ve $^{m}/z$ 369/371 ($M+H^+$)
^{1}H NMR 400MHz ($CDCl_3$) 7.72 (1H, d), 4.83 (1H, d), 1.50 (18H, s).

b) 2-Chloro-5-fluoro-6-methyl-3-pyridinecarbonitrile

To the product from step a) (1.3 g) was added trifluoroacetic acid (2 ml) and diphenyl ether (10 g). The mixture was heated under reflux for 10 min. The mixture was dissolved in *iso*hexane, filtered through silica. And the silica was washed with 10% dichloromethane/*iso*hexane followed by dichloromethane. The dichloromethane layer was evaporated to leave a solid which was triturated with cold *iso*hexane to give the sub-title compound (510 mg).

MS APCI +ve $^{m}/z$ 169/71 ($M+H^+$)
^{1}H NMR 400MHz ($CDCl_3$) 7.64 (1H, d), 2.59 (3H, s).

c) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(3-chloro-5-fluoro-6-methyl-2-pyridinyl)oxy]-2-(2-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound (180 mg) was prepared by the method of Example 8 step b) using the product from step b) and the (2*R*,4*S*) product from Example 8 step a).

MS APCI +ve $^{m}/z$ 463/5 ($M+H^+$).

d) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-6-methyl-3-pyridinecarbonitrile hydrochloride

The title compound (100 mg) was prepared as a white solid by the method of Example 55 step d) using the product from step c). M.p. 148-50 °C.

MS APCI +ve $^{m}/z$ 323 ($M+H^+$).

^{1}H NMR 400MHz (d_6-DMSO) 8.38 (1H, d), 8.12 (4H, bs), 7.85 (1H, d), 7.78 (1H, d), 6.60 (1H, m), 3.70 (1H, m), 3.59 (1H, m), 3.35 (1H, m), 2.52-2.43 (5H, m).

Example 60

4-[[(1R,3S)-3-Amino-1-(3-fluoro-2-thienyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile (E)-butenedioate salt

a) 3-Fluoro-2-thiophenecarboxylic acid.

The sub-title compound was prepared by the method of reference (OPPI BRIEFS, **1997**, *29*, 221-223) to yield the sub-title compound (1.5 g, 40%) as a yellow solid. M.p. 171-172 °C (lit. 172-173 °C).

^{1}H NMR 300MHz ($CDCl_3$) δ 7.52 (1H, dd) and 6.89 (1H, d).

b) 3-Fluorothiophene.

The sub-title compound was prepared by the method of reference (Synth. Comm, **1994**, *24*, 95-101) to yield the sub-title compound (540 mg, 62%) as a clear liquid.

^{1}H NMR 300MHz ($CDCl_3$) 7.20-7.16 (1H, m), 6.85-6.83 (1H, m) and 6.71-6.69 (1H, m).

c) (*4S*)-1,1-Dimethethyl 4-[(*2S*)-2-(3-fluoro-2-thienyl)-2-hydroxyethyl]-2,2-dimethyl-3-oxazolidinecarboxylate.

The sub-title compound was prepared by the method of Example 1 step a) using (*4S*)-1,1-dimethylethyl -2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxyate and 3-fluoro-2-thienyllithium instead of phenyllithium. Purification by chromatography (silica, 10% ethyl acetate/*iso*hexane as eluent) afforded the sub-title compound (500 mg, 28%) as a pale yellow gum.

MS (APCI+ve) m/z 246 $[M(+H)]^+$.

^{1}H NMR 300MHz ($CDCl_3$) 7.07 (1H, dd), 6.73 (1H, d), 5.23 (1H, d), 5.03-4.93 (1H, m), 4.38-4.28 (1H, m), 4.04-3.99 (1H, m), 3.70-3.66 (1H, m), 2.20-2.10 (1H, m), 1.96-1.86 (1H, m) and 1.55-1.52 (15H, m).

d) (*4S*)-1,1-Dimethylethyl 4-[(*2R*)-2-(acetylthio)-2-(3-fluoro-2-thienyl)-2-ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate.

The sub-title compound was prepared by the method of Example 10 step g) using thioacetic acid and the product of step c) instead of thiobenzoic acid and (4S)-1,1-dimethylethyl 4-[(*2S*)-2-hydroxy-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate. Purification by chromatography (silica, 5% ethyl acetate/*iso*hexane as eluent) afforded the sub-title compound (300 mg) as a colourless oil.

MS (APCI+ve) m/z 304 $[M(+H)(-Boc)]^+$.

^{1}H NMR 300MHz ($CDCl_3$) 7.07-7.05 (1H, m), 6.74-6.70 (1H, m), 4.94-4.80 (1H, m), 4.05-3.80 (3H, m), 2.36-2.30 (4H, m), 2.18-2.08 (1H, m) and 1.57-1.47 (15H, m).

e) (*4S*)-1,1-Dimethylethyl 4-[(*2S*)-2-[(5-cyano-2-methoxy-4-pyridinyl)thio]-2-(3-fluoro-2-thienyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxyate.

The sub-title compound was prepared by the method of Example 10 step m) using 6-methoxy-4-(methylsulfonyl)-3-pyridinecarbonitrile and (*4S*)-1,1-dimethylethyl 4-[(*2S*)-2-(acetylthio)-2-(3-fluoro-2-thienyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxyate instead of (*4S*)-1,1-dimethylethyl 4-[(*2S*)-2-(benzoylthio)-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate. Purification by chromatography (silica, 10% ethyl acetate/*iso*hexane) afforded the sub-title compound (100 mg) as a clear gum.

MS (APCI+ve) m/z 394 $[M(+H)(-Boc)]^+$.

^{1}H NMR 300MHz ($CDCl_3$) 8.32-8.30 (1H, m), 7.14-7.10 (1H, m), 6.74-6.70 (2H, m) 5.06-4.64 (1H, m), 4.18-4.08 (1H, m), 4.00-3.85 (4H, m), 3.78-3.48 (1H, m), 2.56-2.15 (2H, m) and 1.58-1.46 (15H, m).

f) 4-[[(*1R,3S*)-3-Amino-1-(3-fluoro-2-thienyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile (*E*)-butenedioate salt

The title compound was made by the method of Example 10 step n) to yield the title compound (56 mg) as a white solid. M.p. 177-178 °C

MS (APCI+ve) m/z 354 $[M(+H)]^+$.
^{1}H NMR 300MHz (*d6*-DMSO) 8.59 (1H, s), 7.55-7.52 (1H, m), 7.02-6.94 (2H, m), 6.47 (2H, s), 5.45-5.39 (1H, m), 3.92 (3H, s), 3.55-3.35 (1H, m), 3.00-2.90 (1H, m), 2.70-2.60 (1H, m), 2.20-2.10 (1H, m) and 2.05-1.95 (1H, m).

Example 61

2-[[(1R,3S)-3-Amino-1-(4-chloro-5-thiazolyl)-4-hydroxybutyl]oxy]-4-chloro-5-fluorobenzonitrile (*E*)-butenedioate salt

a) 2,4-Dichlorothiazole.
The sub-title compound was prepared by the method of reference (Bull. Chim. Soc. Fr., **1962**, 1735) to yield the sub-title compound (7.16 g) as a white solid. M.p. 41-42 °C (lit. 42-43 °C).

^{1}H NMR 300MHz ($CDCl_3$) 7.01 (1H, s).

b) (*4S*)-1,1-Dimethylethyl 4-[(*2R*)-2-(2,4-dichloro-5-thiazolyl)-2-hydroxyethyl]-2,2-dimethyl-3-oxazolidinecarboxylate.
The sub-title compound was prepared by the method of Example 1 step a) using (*4S*)-1,1-dimethylethyl ester-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylic acid and 2,4-dichloro-5-thiazolyllithium instead of phenyllithium. Purification by chromatography (silica, 20% ethyl acetate in *iso*hexane as eluent) afforded the sub-title compound (744 mg) as a pale yellow gum.

MS (APCI+ve) m/z 297/299/301 $[M(+H)(-Boc)]^+$.
^{1}H NMR 300MHz ($CDCl_3$) 5.08-4.98 (1H, m), 4.16-4.04 (2H, m), 3.84-3.71 (1H, m), 2.32-2.22 (2H, m) and 1.61-1.45 (15H, m).

c) (*4S*)-1,1-Dimethylethyl 4-[(*2R*)-2-(4-chloro-5-thiazolyl)-2-hydroxyethyl]-2,2-dimethyl-3-oxazolidinecarboxylate.

To a stirred suspension of palladium on activated charcoal (75 mg) and sodium acetate trihydrate (380 mg,) in MeOH (10 ml) was added a solution of the product from step b) (740 mg) in MeOH (15 ml). The mixture was subjected to an atmosphere of hydrogen (5 bar) for 72 h. The mixture was filtered and evaporated to dryness. The residue was dissolved in dichloromethane (25 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by chromatography (silica, 20% ethyl acetate/*iso*hexane as eluent) afforded the sub-title compound (653 mg) as a colourless gum.

MS (APCI+ve) m/z 363/365 $[M(+H)]^+$.

^{1}H NMR 300MHz ($CDCl_3$) 8.63 (1H, s), 5.20-5.10 (1H, m), 4.18-4.04 (2H, m), 3.91-3.84 (1H, m), 2.27-2.20 (2H, m) and 1.62-1.44 (15H, m).

d) (*4S*)-1,1-Dimethylethyl 4-[(*2R*)-2-(5-chloro-2-cyano-4-fluorophenoxy)-2-(4-chloro-5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylate.

The sub-title compound was prepared by the method of Example 8 step b) using 4-chloro-2,5-difluorobenzonitrile and the product from step b) (650 mg). Purification by chromatography (silica, 20% ethyl acetate/*iso*hexane) afforded the sub-title compound (190 mg) as a pale green foam.

MS (APCI+ve) m/z 416/418/420 $[M(+H)(-Boc)]^+$.

^{1}H NMR 300MHz ($CDCl_3$) 9.10 (1H, s), 7.87 (1H, d), 7.39 (1H, d) 5.98 (1H, dd), 4.19-4.13 (1H, m), 3.99-3.97 (2H, m), 2.58-2.48 (1H, m), 2.20-2.13 (1H, m) and 1.42-1.40 (15H, m).

e) 2-[[(*1R,3S*)-3-Amino-1-(4-chloro-5-thiazolyl)-4-hydroxybutyl]thio]-4-chloro-5-fluorobenzonitrile (*E*)-butenedioate salt

The title compound was made by the method of Example 10 step n) to yield the title compound (136 mg) as a pale yellow solid. M.p. 177-178 °C

MS (APCI+ve) m/z 376/378/380 $[M(+H)]^+$.

^{1}H NMR 300MHz (d6-DMSO) 9.19 (1H, s), 8.03 (1H, d), 7.65 (1H, d), 6.48 (2H, s), 6.17 (1H, t), 3.60-3.48 (2H, m), 3.10-3.06 (1H, m) and 2.37-2.18 (2H, m).

Example 62

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-nitrobenzonitrile hydrochloride

The title compound was prepared by the method of Example 10 step m) & Example 26 step g) using 2-chloro-4-nitro-benzonitrile and the product from Example 10 step g).

MS (APCI+ve) $^m/z$ 344 [M(+H)]$^+$.
^{1}H 400MHz (DMSO-d_6) 8.68 (1H, s), 8.38 (1H, d of d), 8.19 (3H, bs), 7.95 (1H, d), 7.58 (2H, d), 7.39 (2H, m), 7.31 (1H, t), 5.35 (2H, m), 3.2-3.52 (2H m), 2.96 (1H, bs), 2.33 (1H, m), 2.22 (1H, m).

Example 63

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-3-pyridinecarbonitrile-(*E*)-butenedioate salt

a) 2,5-Dichloro-3-pyridinecarbonitrile

To n-BuLi (1.9 ml of a 2.5M solution in hexanes) in Et_2O (4 ml), under nitrogen, at –78 °C, was added a solution of 3-bromo-2,5-dichloro-pyridine (1.08 g) in Et_2O (4 ml) dropwise and stirred for 1.5 h. Solid 1-cyanoimidazole (0.53 g) was added and the reaction stirred for 2 h. After warming to room temperature, water was added and the mixture was extracted with Et_2O. The combined organics were washed with brine, dried (Na_2SO_4) and evaporated to give a black solid (0.64 g). Purification by chromatography (silica, isohexane/ Et_2O as eluent) gave the sub-title compound (0.13 g) as a white solid.

^{1}H NMR 300MHz ($CDCl_3$) 8.56 (1H, d), 7.98 (1H, d).

b) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-3-pyridinecarbonitrile-(*E*)-butenedioate salt

The title compound was prepared by the method of Example 10 steps m & n) using the products from step a) and Example 10 step g).

MS (APCI+ve) $^{m}/z$ 334 $[M(+H)]^+$.

^{1}H 400MHz (DMSO-d_6) 8.80 (1H, d), 8.50 (1H, d),7.50 (2H, d), 7.36 (2H, t), 7.29 (1H, tt), 6.47 (2H, s), 5.32 (1H, dd), 3.44 (1H, dd), 3.35 (1H, dd), 2.79 (1H, m), 2.29 (1H, m), 2.17 (1H, m)

Example 64

β-Amino-δ-[(4-amino-2-nitrophenyl)thio]-(β^1*S*,δ^1*R*)-benzenebutanol

a) 1,1-Dimethylethyl (4*S*) 4-[(2*R*)-2-[(4-amino-2-nitrophenyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The sub-title compound was prepared by the method of Example 10 steps m) using the product from Example 10 step g) and 4-chloro-3-nitroaniline.

MS APCI +ve $^{m}/z$ 374 ($[M+H\text{-boc}]^+$).

b) β-Amino-δ-[(4-amino-2-nitrophenyl)thio]-(β^1*S*,δ^1*R*)-benzenebutanol

The title compound was prepared by the method of Example 10 step n) using the products from step a).

MS APCI +ve $^{m}/z$ 334 ($[M+H]^+$).

^{1}H 400MHz (DMSO-d_6/D_2O) 7.35-7.18 (6H, m), 6.98 (1H, d), 6.72 (1H, dd), 4.54 (1H, t), 3.62-3.36 (2H, m), 2.96 (1H, t), 2.18-2.05 (2H, m).

Example 65

2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-bromo-benzonitrile ethanedioate

a) 1,1-Dimethylethyl (4*S*)-4-[(2*R*)-2-[(4-bromo-2-cyanophenyl)thio]-2-phenylethyl]-2,2-dimethyl-3-oxazolidinecarboxylate

The product of Example 1 step b) (441 mg) was stirred in 7M NH_3 in methanol (10 ml) at room temperature under nitrogen for 6 h. The mixture was then concentrated *in vacuo*, the residue dissolved in DMF (10 ml) and treated with 5-bromo-2-fluorobenzonitrile (200 mg), followed by caesium carbonate (650 mg) under nitrogen. The mixture was stirred at room temperature for 20 h and then partitioned between ethyl acetate and water. The separated aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with brine, and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography (silica, 10% ethyl acetate/*iso*hexane) to give the sub-title compound (332 mg, 64%) as a colourless foam oil.

MS APCI +ve *m*/z 418 $[M\text{-}BOC+2H]^+$.

b) 1,1-Dimethylethyl [(1*S*,3*R*)-3-[(4-bromo-2-cyanophenyl)thio]-1-(hydroxymethyl)-3-phenylpropyl] carbamate

para-Toluenesulfonic acid monohydrate (1 mg) was added to a stirred solution of the product from step a) in methanol (5 ml) under nitrogen, and the mixture was stirred at 20 °C for 48 h. The mixture was diluted with ethyl acetate and washed with 1 M aqueous potassium hydrogensulfate solution, saturated aqueous sodium bicarbonate, brine and then dried ($MgSO_4$) and evaporated. The resulting residue was purified by chromatography (silica, 30% ethyl acetate/*iso*hexane) to give the sub-title compound (175 mg, 57%) as a colourless foam oil.

MS APCI +ve *m*/z 378 $[M\text{-}BOC+2H]^+$.

c) 2-[[(1*R*,3*S*)-3-Amino-4-hydroxy-1-phenylbutyl]thio]-5-bromo- benzonitrile ethanedioate

The product from step b) was deprotected according to the procedure of Example 4 step b) to give the title compound (113 mg, 65%) as a white solid.

MS APCI +ve *m/z* 378 $[M+H]^+$.

^{1}H NMR 300 MHz (D_6-DMSO) 8.11 (1H, d), 7.83 (1H, dd), 7.50 (1H, d), 7.40-7.25 (5H, m), 4.83 (1H, dd), 3.52 (1H, dd), 3.41 (1H, dd), 3.03-2.95 (1H, m), 2.31-2.21 (1H, m), 2.15-2.05 (1H, m).

Screens

The pharmacological activity of compounds according to the invention was tested in the following screens.

Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof, may be screened for nitric oxide synthase inhibiting activity by a procedure based on that of Förstermann *et al.*, Eur. J. Pharm., 1992, 225, 161-165. Nitric oxide synthase converts ^{3}H-L-arginine into ^{3}H-L-citrulline which can be separated by cation exchange chromatography and quantified by liquid scintillation counting.

Enzyme is prepared, after induction, from the cultured murine macrophage cell line J774A-1 (obtained from the laboratories of the Imperial Cancer Research Fund). J774A-1 cells are cultured in Dulbeccos Modified Eagles Medium (DMEM) supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 mg/ml streptomycin & 0.25 mg/ml amphotericin B). Cells are routinely grown in 225 cm^3 flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO_2.

Nitric oxide synthase is produced by cells in response to interferon-g (IFNg) and lipopolysaccharide (LPS). The medium from confluent culture flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 1 mg/ml LPS and 10 units/ml IFNg. After a period of 17-20 hours in culture, harvesting of cells is accomplished by scraping the cell

sheet from the flask surface into the culture medium. Cells are collected by centrifugation (1000 g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20 °C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X-100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors comprising leupeptin (2 mg/ml), soya bean trypsin inhibitor (10 mg/ml), aprotinin (5 mg/ml) and phenylmethylsulphonyl fluoride (50 mg/ml).

For the assay, 25 μl of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400 μM NADPH, 20 μM flavin adenine dinucleotide, 20 μM flavin mononucleotide, 4 μM tetrahydrobiopterin, 12 μM L-arginine and 0.025 mCi L-[^{3}H] arginine) is added to wells of a 96 well filter plate (0.45μM pore size) containing 25 μl of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50 μl of cell lysate (prepared as above) and after incubation for 1 hour at room temperature is terminated by addition of 50 μl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 150 μl of a 25% aqueous slurry of Dowex 50W (Na^+ form) is added to the assay after which the whole is filtered into 96 well plates. 75 μl of filtrate is sampled and added to wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 μl sample which is increased to 1900 dpm in the reagent controls. Compound activity is expressed as IC_{50} (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and aminoguanidine, which gives an IC_{50} (50% inhibitory concentration) of 10 μM, is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained IC_{50} values are calculated. Compounds that inhibit the enzyme by at least 25% at 100 μM are classed as being active and are subjected to at least one retest.

In the above screen, the compounds of Examples 1 to 10 were tested and gave IC_{50} values of less than 10 μM indicating that they are expected to show useful therapeutic activity.

Screen 2

Recombinant human NO synthases (iNOS, eNOS & nNOS) were expressed in *E. coli* and lysates were prepared in Hepes buffer (pH 7.4) containing co-factors (FAD, FMN, H_4B), protease inhibitors, lysozyme and the detergent, CHAPS. These preparations were used, at suitable dilution, to assess inhibition of the various isoforms. Inhibition of NOS was determined by measuring the formation of L-[^{3}H]citrulline from L-[^{3}H]arginine using an adaptation of the method of Förstermann *et al.*[9] Enzyme assays were performed in the presence of 3 µM [^{3}H]arginine, 1 mM NADPH and other co-factors required to support NOS activity (FAD, FMN, H_4B, calmodulin, Ca^{2+}). Since various NOS inhibitors have been reported to exhibit slow binding kinetics, or to inactivate the enzyme in a time dependent manner, enzyme and inhibitor were pre-incubated for 60 min in the presence of NADPH before addition of arginine to initiate the reaction. Incubations continued for a further 60 min before the assays were quenched and [^{3}H]citrulline separated from unreacted substrate by chromatography on Dowex-50W resin in a 96-well format.

In the above screen, the compounds of Examples 1 to 65 were tested and gave IC_{50} values of less than 10 µM against the iNOS enzyme indicating that they are expected to show useful therapeutic activity.

Screen 3

Compounds also show activity against the human form of induced nitric oxide synthase as can be demonstrated in the following assay.

The human colorectal carcinoma cell line, DLD-1 (obtained from the European Collection of Animal Cell Culture - cell line number 90102540) was routinely grown in RPMI 1640 supplemented with 10%(v/v) foetal bovine serum, and 2mM L-glutamine, at 37 °C in 5% CO_2.

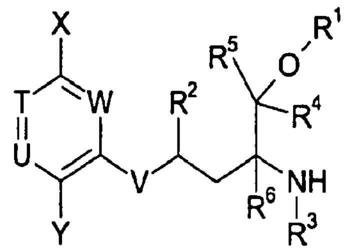
Nitric oxide synthase was induced in cells by addition of medium containing human recombinant gamma-IFN (1000 units/ml), TNF-alpha (200 U/ml), IL-6 (200 U/ml) and IL-1-beta (250 U/ml). After incubation for 18 hours at 37 °C, the medium was removed and the cells washed with warm phosphate buffered saline. Cells were incubated for a further 5 hours at 37 °C / 5% CO_2 in RPMI 1640 containing 100μM L-arginine and 100μM verapamil-HCl in the presence and absence of test compounds.

Nitrite accumulation was determined by mixing an equal volume of culture media with Griess reagent (10 mg/ml sulphanilamide, 1 mg *N*-(1-naphthyl)ethylenediamine in 1 ml 2.5% (v/v) phosphoric acid). Inhibition in the presence of compounds was calculated relative to the nitrite levels produced by untreated cells. IC_{50} values were estimated from a semi-log plot of % inhibition versus concentration of compound.

In this screen the compounds of Examples 1 to 65 gave IC_{50} values of less than 100 μM, indicating that they are predicted to show useful therapeutic activity.

CLAIMS:

1. A compound of formula (I)



(I)

wherein:

X represents H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NH_2, $NHCH_3$, $N(CH_3)_2$, NO_2, CH_2OH, CHO, $COCH_3$ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

Y represents C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO_2, CH_2OH, CHO, $COCH_3$ or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

T, U and W independently represent CR^7 or N; and each R^7 group independently represents H, F or CH_3; and when T represents CR^7, the group R^7 may additionally represent OH, Cl, Br, CN, CH_2OH, NO_2, NHR^{13}, OR^{14} or OSO_2CH_3;

V represents O or $S(O)_n$;

n represents an integer 0, 1 or 2;

R^1 represents H or Me.

R^2 represents C1 to 4 alkyl, C2 to 4 alkenyl, C2 to 4 alkynyl, C3 to 6 cycloalkyl or a 4 to 8 membered saturated heterocyclic ring incorporating one heteroatom selected from O, S and N; any of said groups being optionally further substituted by C1 to 4 alkyl, C1 to 4 alkoxy, C1 to 4 alkylthio, C3 to 6 cycloalkyl, halogen or phenyl; said phenyl group being optionally further substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3, OCF_3, CN or NO_2;

or R^2 represents phenyl or a five or six membered aromatic heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally substituted by one or more substituents selected independently from halogen, C1 to 4 alkyl, C1 to 4 alkoxy, OH, CN, NO_2 or NR^9R^{10}; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

R^3 represents H, C1 to 4 alkyl or C3 to 6 cycloalkyl; said alkyl group being optionally substituted by C1 to 4 alkoxy, halogen, hydroxy, $NR^{11}R^{12}$, phenyl or a five or six membered aromatic or saturated heterocyclic ring containing 1 to 3 heteroatoms independently selected from O, S and N; said phenyl or aromatic heterocyclic ring being optionally further substituted by halogen, C1 to 4 alkyl, C1 to 4 alkoxy, CF_3, OCF_3, CN or NO_2.

R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently represent H or C1 to 4 alkyl;

or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

2. A compound of formula (I), according to Claim 1, wherein V represents O.

3. A compound of formula (I), according to Claim 1, wherein V represents $S(O)_n$ and n represents 0.

4. A compound of formula (I), according to any one of Claims 1 to 3, wherein X and Y independently represent Br, Cl, CH_3, CH_2F, CHF_2, CF_3, OCH_3 or CN.

5. A compound according to Claim 4 wherein Y represents CN.

6. A compound of formula (I), according to Claim 1, which is:

2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;
2-[[(3S)-3-amino-4-hydroxy-1-(3-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;
3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile;
2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethyl)-3-pyridinecarbonitrile;
2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(fluoromethyl)-3-pyridinecarbonitrile;
2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(3-pyridinyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;
2-[[(1R,3S)-3-amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;
2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-isothiazolyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;
4-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;
4-[[(1R,3R)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;
4-[[(1S,3R)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;
4-[[(1S,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methoxy-3-pyridinecarbonitrile;
4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(difluoromethoxy)-3-pyridinecarbonitrile;
2-[[(1R,3R)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;

4-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-($^{2}H_3$)methoxy-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-ethyl-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(1-methylethyl)-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-methyl-3-pyridinemethanol;

6-acetyl-2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridine carbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(hydroxymethyl)-3-pyridine carbonitrile;

2-[[(1R, 3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile;

(β^1S,δ^1R)-β-amino-δ-[(2,5-dichloro-4-pyridinyl)thiobenzenebutanol];

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-fluoro-6-methoxy-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(dimethylamino)-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-(methylamino)-3-pyridinecarbonitrile;

(β^1S,δ^1R)-β-amino-δ-[(5-bromo-2-methoxy-4-pyridinyl)thio]-benzenebutanol;

(β^1S,δ^1R)-β-amino-δ-[(5-chloro-2-methoxy-4-pyridinyl)thio]-benzenebutanol;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-6-ethoxy-3-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-(trifluoromethyl)-2-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-1,6-dihydro-5-methyl-6-oxo-2-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-2-pyridinecarbonitrile;

6-amino-4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-pyridinecarbonitrile;

3-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-methyl-2-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-1-(2-fluorophenyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-1-(4-fluorophenyl)-4-hydroxybutyl]oxy]-6-trifluoromethyl-3-pyridinecarbonitrile;

2(2S)-amino-4 (4R)-(3-fluorophenyl)-4-[(4-methoxy-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(4-chloro-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(5-amino-4-chloro-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(4-hydroxymethyl)-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(4-fluoro-2-nitrophenyl)thio]butan-1-ol;

2(2S)-amino-4(4R)-(3-fluorophenyl)-4-[(3,5-dichloro-2-pyridyl)thio]butan-1-ol;

4-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-3-chlorobenzonitrile;

4-chloro-2-[[(1R,3S)-3-(ethylamino)-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-benzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]oxy]-5-fluoro-benzonitrile;

2-[[(1R,3S)-3-amino-4-methoxy-1-phenylbutyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-4-methyl-1-phenylpentyl]oxy]-4-chloro-5-fluoro benzonitrile;

2-[[(1S,3S)-3-amino-4-hydroxy-1-propylbutyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1S)-1-[(2S)-2-amino-3-hydroxypropyl]pentyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(1S,3S)-3-amino-4-hydroxy-1-(2-methylpropyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(3S)-3-amino-4-hydroxy-1-(5-isoxazolyl)butyl]thio]-6-methyl-3-pyridinecarbonitrile;

2-[[(3S)-3-amino-4-hydroxy-1-(5-isoxazolyl)butyl]oxy]-6-(trifluoromethyl)-3-pyridinecarbonitrile;

2-[[3-(3S)-amino-4-hydroxy-1-(1R)-(2-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[3-(3S)-amino-4-hydroxy-1(1R)-(3-thienyl)butyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-(trifluoromethyl)benzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-pyrimidyl)butyl]thio]-4-chlorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(3-pyridinyl)butyl]thio]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(3-pyridyl)butyl]thio]-4-bromobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(2-thiazolyl)butyl]oxy]-5-fluoro-6-methyl-3-pyridinecarbonitrile;

4-[[(1R,3S)-3-amino-1-(3-fluoro-2-thienyl)-4-hydroxybutyl]thio]-6-methoxy-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-1-(4-chloro-5-thiazolyl)-4-hydroxybutyl]oxy]-4-chloro-5-fluorobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-nitrobenzonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-chloro-3-pyridinecarbonitrile;

β-amino-δ-[(4-amino-2-nitrophenyl)thio]-(β^1S,δ^1R)-benzenebutanol;

2-[[(1R,3S)-3-amino-4-hydroxy-1-phenylbutyl]thio]-5-bromo-benzonitrile;

or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

7. A compound of formula (I), according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, for use as a medicament.

8. A pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. The use of a compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

10. The use as claimed in Claim 9 wherein it is predominantly inducible nitric oxide synthase that is inhibited.

11. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

12. The use as claimed in Claim 11 wherein the disease is inflammatory bowel disease.

13. The use as claimed in Claim 11 wherein the disease is rheumatoid arthritis.

14. The use as claimed in Claim 11 wherein the disease is osteoarthritis.

15. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.

16. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, in combination with a COX-2 inhibitor, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

17. A method of treating, or reducing the risk of, human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, to a person suffering from, or at increased risk of, such diseases or conditions.

18. A method of treatment according to Claim 17 in which it is predominantly inducible nitric oxide synthase that is inhibited.

19. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

20. The method of treatment as claimed in Claim 19 wherein the disease is inflammatory bowel disease.

21. The method of treatment as claimed in Claim 19 wherein the disease is rheumatoid arthritis.

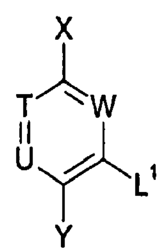
22. The method of treatment as claimed in Claim 19 wherein the disease is osteoarthritis.

23. A method of treating, or reducing the risk of, pain in a person suffering from, or at risk of, said condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

24. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a combination of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, with a COX-2 inhibitor.

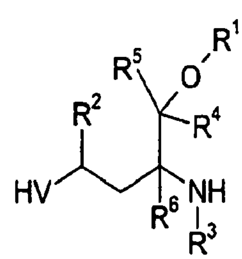
25. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, wherein the process comprises:

(a) reaction of a compound of formula (II)



(II)

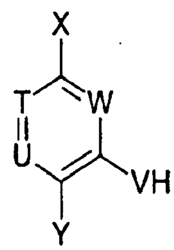
wherein T, U, X, Y and W are as defined in Claim 1 and L^1 represents a leaving group, with a compound of formula (III)



(III)

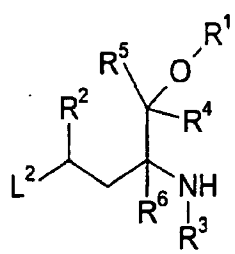
wherein R^1, R^2, R^3, R^4, R^5, R^6 and V are as defined in Claim 1; or

(b) reaction of a compound of formula (IV)



(IV)

wherein T, U, W, X, Y and V are as defined in Claim 1;
with a compound of formula (V)



(V)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Claim 1 and L^2 is a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

(large number of similar references) - same priority #

2000-423357/36 B03 (B02) **AMHP 1998.12.09**
AMERICAN HOME PROD CORP *WO 200034269-A1
1998.12.09 1998-208540(+1998US-208540) *(2000.06.15)* C07D 405/12, A61K 31/33, A61P 31/12, C07D 417/12, 213/75, 213/81
Novel thiourea derivatives useful for treating diseases associated with herpes viruses (Eng)
C2000-128176 N(AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW)

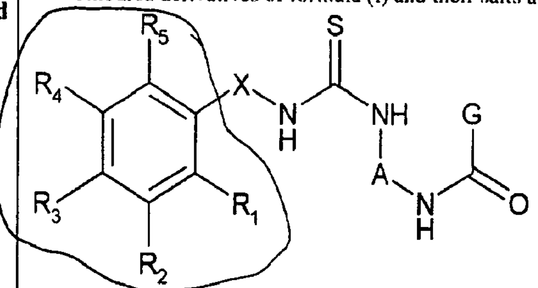
Addnl. Data: BLOOM J D, DIGRANDI M J, DUSHIN R G, LANG S A, O'HARA B M
1999.12.06 1999WO-US28892

B(6-H, 7-H, 14-A2A3) .3

NOVELTY
Thiourea derivatives (I) are new.

reactant II

DETAILED DESCRIPTION
Thiourea derivatives of formula (I) and their salts are new.



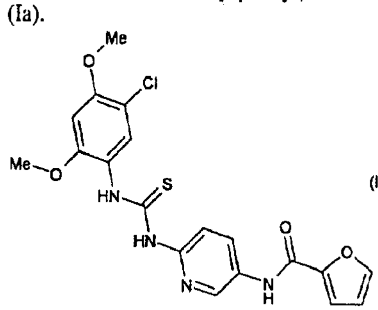
(I)

R_1-R_5 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C perhaloalkyl, 3-10C cycloalkyl, 3-10C heterocycloalkyl, aryl, heteroaryl, halo, CN, NO_2, CO_2R_6, COR_6, OR_6, SR_6, SOR_6, SO_2R_6, $CONR_7R_8$, $NR_6NR_7R_8$, NR_7R_8 or W-Y-$(CH_2)_n$-Z; or
R_2+R_3 or R_3+R_4 = 3-7 membered heterocycloalkyl or heteroaryl;
R_6, R_7 = H, 1-6C alkyl, 1-6C perhaloalkyl or aryl;
R_8 = H, 1-6C alkyl, 1-6C perhaloalkyl, 3-10C cycloalkyl, 3-10C heterocycloalkyl, aryl or heteroaryl; or
R_7+R_8 = 3-7 membered heterocycloalkyl;
A = heteroaryl;
W = O, NR_6 or is absent;
Y = CO or CO_2 or is absent;
Z = 1-4C alkyl, CN, CO_2R_6, COR_6, $CONR_7R_8$, $OCOR_6$, NR_6COR_7, $OCONR_6$, OR_6, SR_6, SOR_6, SO_2R_6, $SR_6NR_7R_8$ (sic), NR_7R_8 or phenyl;
G = aryl or heteroaryl;
X = bond, NH, 1-6C alkyl, 2-6C alkenyl, 1-6C alkoxy, 1-6C thioalkyl, 1-6C alkylamino or CHJ;
J = 1-6C alkyl, 3-7C cycloalkyl, phenyl or benzyl; and
n = 1-6.

ACTIVITY
Virucide. In a V2V antiviral (ELISA) assay N-{2-(5-chloro-2,4-dimethoxy- phenyl)-thioureido]-pyridin-3-yl}-2-fluorobenzamide inhibited viral replication by 90% at a concentration of 10 micro g/ml.

USE
(I) are useful for inhibiting the replication of a herpes virus and treating herpes virus infections such as human cytomegalovirus, herpes simplex virus, and varicella zoster virus (claimed). (I) are also useful for inhibiting and/or treating diseases associated with herpes viruses including Epstein-Barr virus, human herpes viruses-6 and -7, and Kaposi herpes virus.

SPECIFIC COMPOUNDS
31 Compounds (I) are claimed e.g. furan 2-carboxylic acid {6-[3-(5-chloro-2,4-dimethoxy-phenyl)- thioureido]-pyridin-3-yl}-amide (Ia).



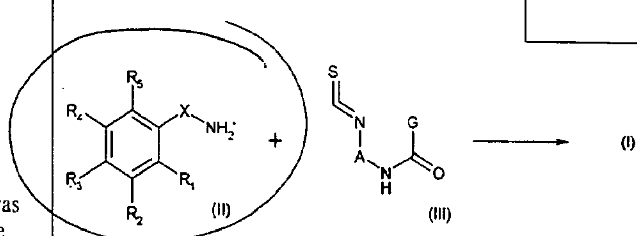
(Ia)

2000-423357/36

ADMINISTRATION
Dosage is 0.01-1000 mg/kg/day orally or 0.1-100 mg/kg/day parenterally.

EXAMPLE
To a solution of 2,5-dichloroaniline (0.16 g) in THF (20 ml) was added freshly prepared 1,1'-thiocarbonyldiimidazole (0.2 g) and the mixture was stirred for 30 minutes at room temperature. [1,2,3]-Thiadiazole-4-carboxylic acid (4-amino- phenyl) amide (0.22 g) was added and the mixture was stirred for 6 hours. Work up gave [1,2,3] thiadiazole-4-carboxylic acid {4-[3-(2,5-dichlorophenyl)-thioureido]-phenyl}-amide.

TECHNOLOGY FOCUS
Organic Chemistry - Preparation: (I) can be prepared by reacting appropriately substituted amines of formula (II) with appropriately substituted isothiocyanates of formula (III).



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